T.R.N.C

NEAR EAST UNIVERSITY
INSTITUTE OF HEALTH SCIENCES

Prevalence Study Of Antibiotic Usage And Health Care Associated Infections At Near East University Hospital In Northern Cyprus

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

BY:

WISSAL MOHAMED JAME

In partial Fulfillment Of The Requirements For The Degree Of
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Advisor:

Assoc. Prof. Bilgen Basgut

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DEDICATION

This thesis is dedicated to my husband, Waled, who has been a constant source of support and encouragement during the challenges of graduate school and life. I am truly thankful for having you in my life.

To my daughters, Mayssa and Maria, not a day did you complain about how busy I was. I thank you for your understanding and patience.

To my parents, for providing me with unfailing support and continuous encouragement throughout my years of study and through the process of researching and writing this thesis. This accomplishment would not have been possible without them. Thank you.

Approval

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ABSTRACT

Objective: This study aimed at providing a prevalence survey of antibiotic usage pattern and antibiotic therapy cost, and estimate health care associated infection at Near East University hospital.

Methodology: By using period prevalence method, this study was conducted to estimate antibiotic usage and prevalence of hospital acquired infection through inpatients in surgery, medicine, paediatrics and ICU at the hospital in April 2016. The desired data on antibiotic and HAIs were registered using pre-prepared survey. Appropriateness of antibiotic was evaluated according to the indication of antibiotic use, dose, the spectrum of antibiotics, dose frequency and dosage regimen.

Results: Of 137 inpatients, 54 (39.4%) were on one or two antibiotics. Among patients receiving antibiotics, 7 were on surgery ward, 35 were on medicine ward, 6 on pediatric ward and 6 on ICU unit. The usage of antibiotic was appropriate in 38(70.4%) patients and inappropriate in 16(29.6%) patients. The most common inappropriate use of antibiotic was 37.1% through patients on medicine wards. The most prevalent cause of inappropriate usage was improper choice of the right antibiotic after getting the result of AST and prolonged empirical use of broad spectrum antibiotics without presence of clear diagnosis. At the time of analyzing the appropriate use of antibiotic according to indication, it was found out that, the most prevalent appropriate use was for empirical (80.6%) and prophylaxis (69.2%), while the most common reason why antibiotic was used inappropriately was for definitive therapy (60.0%). During the study period, 59 antibiotics were used by 54 patients and (88.9%) of them prescribed by I.V rout. the most commonly used antibiotic was cephalosporin 29 (49.2%). Overall, 15(10.9%) of hospitalized patients with hospital acquired infections, ranging from 11 (12.8%) in medicine to 4 (33%) in intensive care unit. The most prevalent infections was urinary tract infections 5(33.3%) and blood stream infections 3(20%). The most prevalent isolated bacteria in patients with nosocomial infections was Staphylococcus species. Prevalence of HAIs was high in patients over 30 years old and in those in hospital more than 10 days. The overall daily cost of antibiotic therapy in one day was

($919.61) while the total daily cost for nosocomial infections was ($ 482) and the mean daily cost per patient was ($17.02) and mean daily cost per patient with hospital infections was ($32.13). The mean daily cost per patient was ($ 8.12) in surgical wards, ($21.57) in medical wards, ($ 6.94) in pediatrics and ($5.79) in ICU ward.

Conclusion: This survey showed that the rate of inappropriate use of antibiotic in our hospital was low when compared with other studies and antibiotic usage rates which was detected in this study was relatively low and this is may be due to the low number of total hospitalized patients. Definitive therapy is still a major problem, Also widely use of broad spectrum antibiotics as empirical therapy without culture result to guide therapy was determined in this study.
The prevalence of HAI was relatively high in this centre as a private hospital and this type of infections are an important part of extra costs in the hospital.

Keywords:- Antibiotic, prevalence, HAIs, rational use.

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LIST OF ABBREVIATIONS

NO	ABBREVIATIONS	EXPLANATION
1	ADR	Adverse drug reactions
2	AMR	Antimicrobial resistance
3	AST	Antibacterial susceptibility test
4	CART	Council for Appropriate and Rational Antibiotic Therapy
5	CDC	Centre for disease control and prevention
6	CDIs	Clostridium difficult infections
7	ECDC	European center for disease control and preventions
8	ESR	Erythrocyte sedimentation rate
9	GAS	Group A streptococcus species
10	GIT	Gastro intestinal tract
11	HALs	Hospital acquired infections
12	HCAIs	Health care associated infections
13	HCAIs	Hospitals in Europe Link for Infection Control through Surveillance
14	ICU	Intensive care unit
15	IV	Intravenous
16	MIC	Minimum inhibitory concentration
17	ORS	Oral rehydration salt
18	PD	Pharmacodynamics
19	PK	Pharmacokinetics
20	PS	Prevalence survey
21	SPSS	Statistical Package for Social Sciences software
22	UTIs	Urinary tract infections
23	WHO	World health organization

GENERAL INTRODUCTION:

The bacteria which causes infection can be prevented, managed and treated through anti-bacterial group of compounds known as antibiotics. These agents are synthetic, semi-synthetic or natural compounds that kill or inhibit the growth of bacteria. When bacteria are exposed to an antibiotic, their response may be one of the following:

1. They are sensitive and antibiotic causes the inhibition of their growth, division and death.

2. They can remain unaffected or resistant.

The word of **Antibiotics** sends terror coursing through the veins of students and makes many healthcare professionals uncomfortable. In fact an antibiotics category include several classes of drugs that differ in spectrum of activity, pharmacokinetics pharmacodynamics, adverse effect and clinical utility.(Jason C. et al, 2012).

For years we have believed that taking a reasonable, stepwise way for pharmacotherapy learning process of infectious diseases can help burn away the mental fog preventing optimal use of these drugs, but learning the characteristics of antibiotics simplifies learning infectious disease pharmacotherapy.(WHO, 1977).

Antibacterial agents bring about a dramatic variation for the treatment of infectious diseases but also it affects the fate of humankind. Antibiotics chemotherapy made advances, resulting in the optimistic view that infectious diseases would be conquered in the near outlook. But, actually, infectious diseases emerging have left us facing a countercharge from infections.
(Tommo SAGA. et al, 2009).

There were usually a relationship between beginning of the modern “antibiotic era” with the names of **Paul Ehrlich** and **Alexander Fleming**. (A arestrup FM. et al, 2001).

The pre-antibiotic era started in 1910, by discovering the first antimicrobial agent **salvarsan** by **Paul Ehrlich** and continued to 1928, when Fleming discovered penicillin. (A arestrup FM. et al, 2001, Inglis GD. et al, 2005).

During the subsequent two conventions, a novel type of antibiotics were developed one after another, leading to a golden age of antimicrobial chemotherapy which continued until 2010, (Luangtongkumt. et al, 2006) as shown in the figure below.

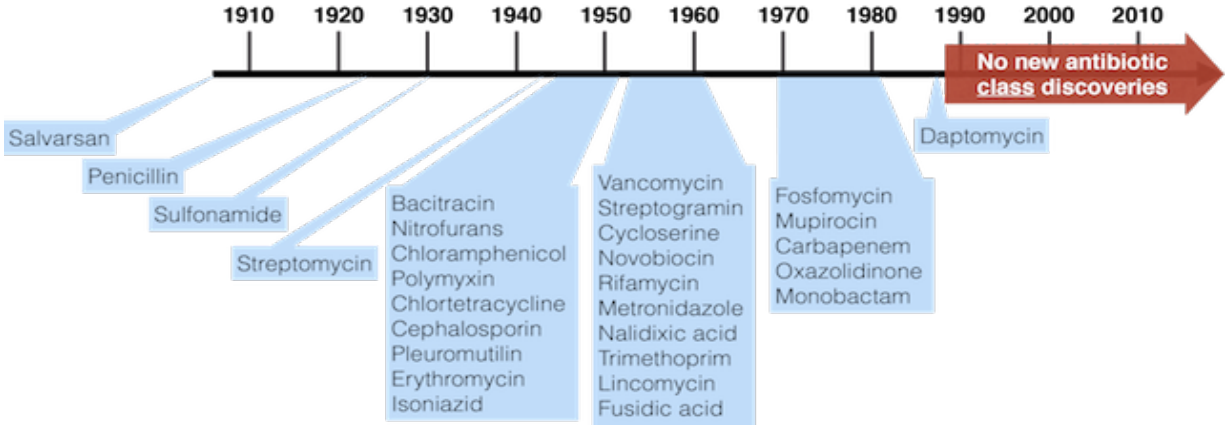


Fig No.1 The Development Of Antibiotics Discovery.

After the golden age of antimicrobials just by few years, warning signs of developing resistance were observed. More and more bacteria with multiple drug resistance are also being observed. Various reports support the contention that the abuse and misuse of antibiotics is largely responsible for the developing resistance problem. (Mellon, M. et al, 2001).

‘Antimicrobial resistance poses a catastrophic threat. If we don’t act now, any one of us could go into hospital in 20 years for minor surgery and die because of an ordinary infection that can’t be treated by antibiotics. And routine operations like hip replacements or organ transplants could be deadly because of the risk of infection.’
(Professor Dame Sally Davies, England’s Chief Medical Officer, speaking about her 2013 Annual Report).

Prevalence surveys consider a useful tool to measure and monitor the burden of hospital acquired infections (HAI) and antimicrobial usage rate. (Luangtongkumt. et al,

2006). A specified number of outcomes in a population can be measured by prevalence survey at a specific period of time. The period of time may be a week, month or season.

This method can be used to describe the burden of all HAI types on health services when compared with the incidence surveillance, which focus on single microorganisms or infection types. PS when repeated can also provide useful data on efficacy of infection prevention and control measures. (Luangtongkumt. et al, 2006).

This surveillance method is also a practical method for monitoring and investigation of patterns of antimicrobial prescribing in the absence of electronic hospital prescribing. Prevalence surveys can support identification of areas on specific agents or within particular clinical areas, allow differences between hospitals to be identified or warrant identity of changes in manner of prescribing over time. (UN. general accounting office, 2004).

OUTLINE OF THE THESIS:

The main objective of the study presented in this thesis is to estimate the usage of antibiotics, both appropriate and inappropriate usage, in an educational hospital in Northern Cyprus.
Also we determine the prevalence of hospital acquired infections (HAIs).

This study is the first of its kind in Northern Cyprus, and it's supposed to be of much value for pharmacy faculties to understand the approaches regarding the rational use of antibiotics that is used in hospitals in Northern Cyprus.

This particular thesis has been divided into two sections consisting of a brief information and literature review, which has been discussed in detail and with care in part one and has been followed with the aim of the study, methods and materials used during the research and then has continued with the outcome and discussion of the feedback received in part two. Last but not least, a brief conclusion has been presented through the end of the study.
The chapter of literature review has been divided into four sections respectively:

The first section mainly focused on health care system discussing the ways of approaches to access health facilities and investigated the meaning of infectious diseases.

In the following section, the general concept of essential medicines has been summarized and the meaning of rational use of drugs that include the rational process of prescribing has been addressed with the meaning, effect and examples on irrational drug use.

The rationality of antibiotics, appropriate and inappropriate prescribing of antibiotics, adverse effect of antibiotics misuse, The most important situation where antibiotic was used irrationally, interventions to improve appropriate usage of antibiotics have been mentioned in the third section which antibiotic stewardship program has also been discussed briefly and respectively.

In the fourth section, some considerable previous PS study on antibiotic usage and infectious disease that conducted in different nations worldwide have been addressed as the final stage of the thesis.

LITERATURE REVIEW

1. Health Care System:

Almost all countries want to meet the health and medical needs of their populations. In the face of varied cultural, political, economic, epidemiologic, environmental, and demographic forces, each country tries to tailor its health care system to the special characteristics and requirement of its population. Yet the building blocks are largely the same, every country requires a basic public health foundation, which is in developing countries may depend on the community health staff. Developed countries require clinicians, nurses, and other health care professionals, hospitals and clinics, and effective methods to pay for both clinical services and medicines, medical devices, and other interventions.

In order to improve the care provided and to ensure that the service is meeting the patients' demand, all the countries require several ways to measure the effectiveness of the provided care. These ways are needed by the country to evaluate treatments and health care interventions and to educate clinicians about health and medicine, and to help their populations to get healthy lives, make the best health care decisions, participate in their own care and definitely with lowest cost of health care system provided. (Stephen Morrissey. et al, 2015).

1.1. Access To Health Care:

The meaning of access to health care means " having the timely use of personal health services to achieve the best health results". (Stephen Morrissey. et al, 2015).

There are three steps required to access to health care system:

1- Gaining entry to health care system.
2- Getting access to the care sites where patients can get their needed service.
3- Finding providers who meet the need of individual patients and with that patients can establish a relationship based on trust.

Measuring health care access can be done in several ways:

1- Measuring the presence or absence of specific resources which facilitate health care, such as health insurance.
2- Patient assessment of how they can get access to health care.
3- Measuring outcomes of good access to care (successful receipt of needed service. (Rockville, MD, 2014).

1.2. General Approach To Infectious Disease:

The infectious disease pharmacotherapy makes a confusion towards many clinicians, but the approach to the patient with an infection is simple and consistent. By understanding this approach, the first step in developing a useful expertise in infectious diseases and antibiotic use is considered.(ISDA, December 2010).

Technically the term **antibiotic** refers only to a group of antibacterial drugs that are natural products while **anti-infective and antimicrobial** include antibacterial, antifungal, antiviral. Because **antibiotic** is the most commonly used term, we will use it to refer to antimicrobials in general or antibacterial specifically. (Jason C. et al, 2012).

Healthcare-associated infections (HCAIs) are infections that are associated with devices, procedures or interventions that are carried out in healthcare facilities. There are two approaches to assessing the burden of HCAI – continuous (incidence) surveillance or prevalence ('snapshot') surveys (PS). (Fabry J. et al. 2007).

1.2.3. Risk Factors For Health Care Associated Infection:

The most common risk factors that may increase prevalence of HAI include:

1-surgery: the duration and surgery type also have an effect on development of nosocomial infections.

2-length of stay: longer hospital stay can increase the risk for infections especially when the patient is admitted to hospital for multiple illnesses

3-antibiotics: Irrational and overuse of antibiotics can lead to development of bacterial resistance.

4- Hygiene techniques: Insufficient practice of hand hygiene among patients and hospital staff may increase risk for infections.

5- Invasive procedures: It can introduce infection into the body, for example, urinary catheters, mechanical ventilator, IV drips and infusions.

6-Age: younger and elderly patients are more susceptible to infections due to impaired immune system function.

7- Areas with high-risk: Intensive care units (ICU) are more likely to have infection.

1.2.4. The Consequence Of Hospital Associated Infections:

1- Create additional suffering and come at a high cost for patients.

2- Extend hospital stays.

3- Increase resistance to antibiotic.

4- Represent a large additional fiscal burden for health systems.

2. Concept Of Essential Drugs:

The World Health Organization's (WHO) policies on drugs are based on the essential drugs concept and the first WHO Model List of Essential Drugs was issued in 1977.
(WHO, 1977).

The meaning of essential drugs is that agents meet the required health care of the population. It relies on the health relevance of the public, safety, efficacy and cost-effectiveness. These medicines must be available within the health care systems at all times in sufficient amounts, in the appropriate dosage forms, adequate information, and with cost that is suitable for individuals and the community.

The first step toward the improvement of the quality of health care facilities must be a correct choice of essential medicines. The process of picking of medicines must be followed by appropriate use. Around the world more than 50%

of all drugs are prescribed and dispensed inappropriately, and 50% of patients cannot take these drugs in the correct way. In addition, one-third of the world's population fails to access the essential medicine. So the effective medicines of yesterday became ineffective today because of inappropriate use. (MC Donald LC. et al, 2001).

2.1. General Concept Of Rational Use Of Medicines:

According to WHO rational use of a drug means the patients receiving the medicine that is appropriate, in doses which meet their individual requirement, for an adequate period of time, at the lowest cost, both to them and the community. (WHO, 1985). The rational prescribing should meet the following criteria:

- Appropriate indications.
- Appropriate Drug (right dose, dosage form and rout of administration).
- Appropriate Patient.
- Appropriate Information to the patient.
- Appropriate Monitoring.

2.1.1. The Process Of Rational Prescribing:

The rational prescribing process has been divided into six steps as follows;

Step 1: Specify the problem of the patients.

Step 2: Define the therapeutic objective (what is the goal of the therapy).

Step 3: Identify the suitability of your treatment by:

i. Defining the correct diagnosis.
ii. Making an inventory of effective groups of drugs.
iii. Choosing an effective group according to criteria (safety, suitability and cost of the drug).
iv. Choosing a drug.

Step 4: Start the treatment.

Step 5: Give information, instructions and warnings.

Step 6: Monitor (and stop) treatment.(T.P.G.M. de vries. et al, 1994).

2.2. Irrational Use Of Drugs:

It means one or more of the above conditions is not met. It was calculated that half of the drugs are sold or dispensed inappropriately. (WHO, 1985). Also half of the patients fail to take the medicines as prescribed by the physician. Irrational use may include Poly pharmacy, overuse of antibiotics, failure in prescribing appropriate drugs according to clinical guidelines.(ABID ULLAH. et al, July 2013).

2.2.1. Examples On Irrational Use Of Drugs:

Irrational medicine occurs in all countries and in all setting for health care from hospitals to homes. It involves cases in which no medicine is needed but prescribed. (Nausheen,S. et al, 2013).

1- Poly pharmacy: It occurs when the patient use more medicine than necessary.

2- No medicine needed: Many times, medicine is used unnecessarily. Use of medicine when not needed involves many no therapeutic uses.

3-Wrong medicine: For various reasons, the wrong medicine may be prescribed and dispensed.

4- Ineffective medicine and medicine with doubtful efficacy: Medicines that are ineffective sometimes are given to patients because of common practice or because the patient thinks that the more prescribed medicine, has better effect.

5- Unsafe medicine: The likelihood of adverse reaction outweighs the therapeutic effects when unsafe medicines are prescribed.

6- Under use of available effective medicine: Several studies have shown that ORS was prescribed for only a small number of children with acute diarrhea.

7- Incorrect use of medicine: For instance; a frequent incorrect use of antibiotics is given to a patient only one or two days of antibiotic supply rather than the full course of therapy.

2.2.2. Impact of irrational use of medicine:

Inappropriate use of medicine on a wide scale can have significant side effects on health care costs, the quality of drug therapy and medical care. (Nausheen,S. et al, 2013).

1- Impact on quality of medicine therapy and medical care: It is leading to increased morbidity and mortality.

2- Impact on antimicrobial resistance.

3- Impact on cost: Increase of the cost due to waste of the resources.

4- Psychosocial impact: For example, when patients have some beliefs like " There is a pill for every ill" this may cause increase in the demand of drugs.

3. Rationality Of Antibiotics:

Some facts on antibiotics:

1. The resistance of antibiotics is one of the world's most pressing public health threats.
2. One of the most important tools by which we have to combat life-threatening bacterial diseases is antibiotics, but using antibiotics can cause side effects.
3. Misuse or overuse of antibiotics can increase the development of drug-resistant germs.

In order to get effective strategies for improving antibiotic, all the members of health care system including (Patients, healthcare providers, hospital administrators, and policy makers must work together to improve medical care and save lives. (CDC, Center for Disease Control and Prevention, 2011).

3.1. Appropriate Prescription Of Antibiotics:

To choose appropriate antibiotics we have to answer the following questions:

1- Is antibiotics necessary?

Antibiotics are only necessary for, bacterial infection and not all infections are caused by bacteria. Most of the infection are caused by viruses and antibiotic may not treat viral infection or prevent secondary bacterial infection in patients. If the infection is minor and it is due to bacteria, then it is not necessary to prescribe antibiotics because most of the simple infections are overcome by themselves. Antiseptic may be used locally in minor superficial infection. However, in the presence of abscess, then the pus must be drained surgically and if sufficiently drained then there is no need antibiotics. (VKE, Lim. et al, 1993).

2- How should the correct or proper antibiotics be chosen?

There are various factors that must be taken into account when antibiotics are selected. It is well known that the outcome from antibiotic depends upon proper selection of antibiotics. (VKE, Lim. et al, 1993). The three major factors are:

i- Determination of microbial agent: The characteristics of pathogenic microbes that have an effect on the route and duration of antibiotic therapy include virulence and resistance patterns, and whether the pathogen is intracellular or extracellular are very important to take into account when choosing an antibiotics. (WJ. MC Issac. et al, 1998).

When a pathogenic microorganism is identified, the next step which must be taken by the physicians is the performance of antimicrobial susceptibility testing (AST). This test measures the ability of a particular organism growing in the presence of a specific drug. The main goal of AST is to expect the success or failure of the selected antibiotic. Then, the result of AST which is in the form of minimum inhibitory concentration (MIC), is interpreted by the laboratory as resistance, susceptible or intermediate, based on the clinical and laboratory standard. (ATS Guidelines for the Initial management of adults with community acquired pneumonia, 1993).

ii- The patient: There are many factors performed (Kunin CM. et al, 1973).
related to the patient that traditionally influence antibiotic selection decisions. These are as follows:

1. The severity of illness*:* For instance, impaired renal and hepatic function. During antibiotics administration it is important to determine how the kidney and liver work because they are primary organs that are responsible for removal of drugs from the body. However, dose may be reduced to avoid accumulation and toxicity in patients with reduced renal or hepatic function. In contrast, dose might need to be increased to avoid under-dosing in young healthy patients who have rapid hepatic metabolism or rapid renal elimination.

2. Patient's age: Almost all of pediatric drug dosing of antibiotics is guided by weight while in geriatric patients, the level of creatinine in the serum alone does not reflect the function of kidney and the clearance of creatinine should be estimated according to the weight of these patients.

3. Genetic Variation: Susceptibility of the genetic materials to the adverse effects of antimicrobial agents was observed for several antimicrobial agents, so before administration of certain drugs, it is important to make an appropriate testing for this variation.

4. Pregnancy and Lactation*:* When using antimicrobial agents in pregnant women, a specific consideration must be taken into account which is related to both the pregnant woman and her baby. Increases in plasma volume and renal blood flow, particularly in the third trimester in the pregnant woman can result in more rapid clearance and lower serum levels of large number of medicines, particularly antimicrobial agents.

5. History of Allergy to antibiotics: An allergy or intolerance history must be routinely obtained in the diagnosis and management of infection.

6. History of Recent Antimicrobial Use: If the patients' exposure to antibiotics has been recent (approximately 3 months), this can help the physicians to select an appropriate antimicrobial therapy. This is because the microorganism that causes the current infection may have a resistant to that drug, and an alternative agent should be used.

iii- The antibiotics: The properties of antibiotics itself can affect the selection of antibiotics which include dosing schedule, bioavailability, spectrum of antibiotics that contains both narrow spectrum affecting the gram negative only or broad spectrum antibiotics which affect both gram positive and gram negative bacteria, patient tolerance, antibiotics effects (bactericidal or bacteriostatic). Bactericidal agents, which kill and cause disruption of the bacterial cell, include drugs which act on the cell wall (e.g, b-lactams), cell membrane (e.g, daptomycin), or bacterial DNA (e.g, fluoroquinolones) while Bacteriostatic drugs prevent bacterial growth by inhibiting replication without killing the bacteria. The Most considerable example on bacteriostatic agents, including sulfonamides, tetracyclines, and macrolides which act by inhibiting protein synthesis. However, some agents act as bactericidal against specific type of bacteria and may bacteriostatic against others and vice versa.

Pharmacokinetics and pharmacodynamic properties act together with host factors, therefore this may also be considerable in determining a dosing regimen. Especially, this relates to the concept of concentration-dependent vs. time-dependent killing. (Niederman MS, 2005).

In addition to the purchase price of a particular agent, the cost of an antibiotics is based on many factors that include administration costs, prolonged hospitalization, adverse effects consequence, serum concentration monitoring and clinical efficacy.

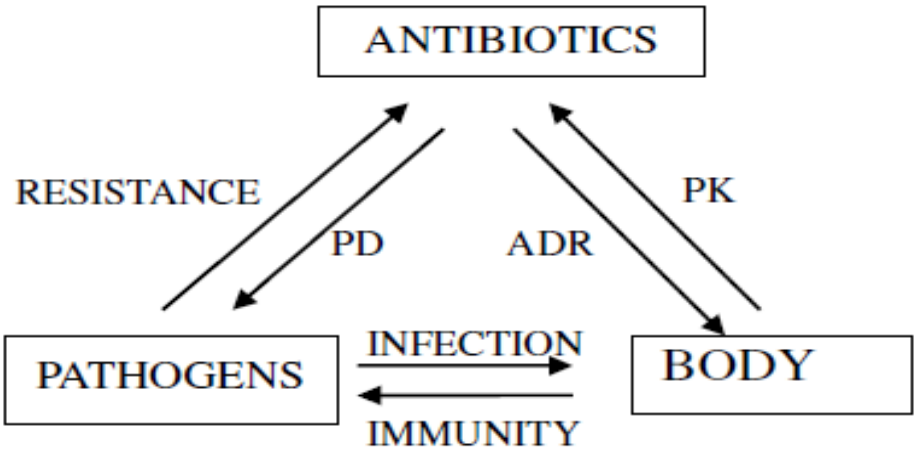


Fig. 2. Diagram of antibiotics- pathogens - body relationship. PD : pharmacodynamic ; PK : pharmacokinetic ; ADR : adverse drug reaction

3- What are the antibiotics indications?

There are three indications for the antibiotics therapy:

- **Definitive Therapy:** It is for accurate diagnosis of bacterial infection. Antibacterial agents are potent against bacteria and it is considerable to restrict only for treatment of bacterial infections. So it is important to take the sample either blood or fluid secretion and test it on the basis of clinical testing (i.e. susceptibility test). It allows testing microorganisms to recognize narrow spectrum, least toxic and cheap antibiotics. (Nathwani D. et al, 1990).

- **Empirical Therapy:** It is also known as Blind therapy of antibiotics and it should be given in certain critical condition which requires immediate use of antibiotics

before any laboratory findings available. For example, sepsis syndrome, hectic temperature, raises ESR etc. The most appropriate class of antibiotic should be prescribed are broad spectrum antibiotics in such critical conditions. For instance, combination of amoxicillin and gentamicin, both, act on gram positive and gram negative microorganism. (Pinto Pereira LM. et al, 2004).

- **Prophylactic Therapy:** The patients having risk of infection should take a prophylactic antibiotics and it is divided to:

i- Non surgical prophylaxis : For example, antibacterial prophylaxis should be given to avoid transmission of pathogens to susceptible contacts, antimicrobial prophylaxis before dental and other invasive procedures in patients having high susceptibility to bacterial endocarditis and traumatic injuries with a high probability of infectious complications. (Cusini A. et al, 2010).

ii- Surgical prophylaxis: This is given mostly as a single dose before the surgery and this type of prophylaxis is used to reduce the occurrence of postoperative surgical site infections. It is usually given to patients who are undergoing operation related to high rates of infections, those involving implantation of prosthetic material. (Slama TG. et al, 2005).

3- What are the most correct route, dose, frequency and duration of selected antibiotic?

The select of an appropriate antibacterial regimen depends on indication of antibiotic therapy. For example, in surgical prophylaxis it is preferred to give antibiotics by IV rout with single dose. Also oral therapy is preferable because it is effective for the most indications. It is cheaper, more convenient, reduced catheter infection risk while intramuscular route is dubious and intravenous administration is used for severe disease of specific location. (Kim B-N, 2005).

4- Is the treatment effective?

This must be determined after starting of antibiotics therapy course and the outcomes must be measured to estimate the appropriate use of antibiotics. There is some consideration for continuing antibiotics therapy including duration of antimicrobial therapy, response of patient to treatment, adverse effects of antibiotics. (Surbhil Leekha. et al, February 2011).

3.2. Inappropriate Use Of Antibiotics:

Inappropriate and incorrect use of antibiotics occurs in both developing and developed countries. Physicians may prescribe antibiotics to patients who do not need them and the patients may do not commit to their treatment which is leads to increase risk of resistance to therapy. Two thirds of all antibiotics are sold without prescription, through unregulated private sectors. (Kathleen Holloway. et al, 2011). Low adherence levels by patients are common. Many patients taking antibiotics in under-dose or for shortened duration. For example, take the drugs for 3 days instead of 7 days.

The infectious diseases are threatening the health of populations. If antibiotics become ineffective, these diseases will lead to elevation in the use of health-care facilities, premature mortality and morbidity. While resistance to older antibiotics is increased, new generations' development of antibacterial is stopping. (Kathleen Holloway. et al, 2011). Therefore, efficient use of existing antimicrobial agents is required to make sure that the long term of effective treatment of bacterial infections is available. Both restrictive and appropriate use are included in efficient use of antibiotics.

3.2.1. Aspects Of Inappropriate Use Of Antibiotics:

1- No indication for antibiotics use.

2- Wrong selection of antibiotics.

3- Use of antibiotics in inappropriate dose, rout, durations, etc.

4- Inappropriate combination.

5- Unnecessary use of the costly antibiotics.

3.2.2. Irrational Antibiotics Use Determinants:

It is important to understand the reasons why providers and consumers behave the way they do, in order to promote rational use of antibiotics. (Kathleen Anne H, 2011). The following reasons explain why people use antibiotics irrationally**:**

- Poor knowledge of the provider especially regarding the prescribers who are insufficiently qualified or supervised.

- The habit of prescriber, it may take time to look up guidelines for prescribing.
- Lack of self-covering medicines information like drug bulletins and clinical guidelines.
- Poor availability of government-funding for education and supervision of medical staff which includes prescribing process.
- The consultation time is very short, which does not allow sufficient time to make a good diagnosis.
- Patient-dispenser interaction time also is very short (may be seconds) that does not allow sufficient time to explain to patients how to take their medicines.
- Inappropriate prescribing norms due to peer pressure. For example, where doctors fear to be prescribing differently to their fellows, especially if those fellows are senior consultants.
- Patient demand in reality and it is recognized by prescribers (who may understand a greater demand than the real demand).
- Lack of diagnostic support services such as laboratory services.
- Progressing process is poor. For example, the inability to follow-up of patients.
- The medicines supply is inappropriate. For example, where inappropriate antibiotics are supplied, available and appropriate ones are not.

3.2.3. The Most Common Situations Where Antibiotics Are Used Irrationally:

There are three situations where antibiotics are usually prescribed irrationally; fever, sore throat and diarrhea.

1-Fever: Hundreds of diseases were manifested by high temperature. Antibiotics do not have any beneficial effects in cases of fever due to non-bacterial causes. Viral infections are the most common infectious causes of fever and antibacterial drugs do not play any role in their management. They neither shorten the duration of the illness nor prohibit secondary infections. Indistinctive use of antibiotics in all cases of fever adds to the cost of therapy, adverse effects, and development of drug resistance and may mask the signs of bacterial infection, making a proper diagnosis

difficult. High grades of fever may be managed with antipyretics like paracetamol and it should never be forgotten that antimicrobials are NOT antipyretics. (Del Mar CB . et al , 1977).

2-Sore throat: It is probably the most common illness where antibacterials are misused. Although 15% of all office visits are accounted for sore throat, it has been found that in various studies only 8 to 20% of patients with a sore throat visit a general practitioner, while 80-90% of them can be cured. Approximately, 20% of outpatient will have group A Streptococci on throat culture and the other 80 % will have a negative sore throat culture, but using clinical judgment alone will mean that roughly 40% of those patients will receive antibiotics. (Danchin MH. et al, 2002).

The result of the survey was conducted by physicians in 17 European countries that fever in patients with tonsillitis resolved itself with or without therapy in two or three days as long as routine use of antibiotics in cases of sore throat is often uncalled for.

The method of Sore Throat was developed by a group of American Emergency Room Physicians for the diagnosis of pharyngitis that is caused by group A Streptococcal species, which can be useful in making a correct diagnosis of this infection, especially in adults and may help in decisions about antibacterial use. (Linder JA. et al, 2005). It includes the following four signs:

1. Tonsillar exudates.
2. Swollen anterior cervical nodes.
3. A history of a fever of more than 38^0 C.
4. Lack of a cough.

If the score is one or less about 45% of patients and chance of GAS is less than 10%, only symptomatic treatment is fixed and if scores two and three, approximately 45% of patients, and chance of GAS is 14-34%, a throat swab culture should be taken and only symptomatic treatment should be prescribed until the culture report is available. If the score is four, only 10% of patients, and chance of GAS is 56%, a throat swab culture should be obtained, and then antibiotics can

be started if the situation demands. By following this easy method, about 70-80% of prescribed antibiotics for sore throat can be avoided every year.

3-Diarrhoea: This is the third condition where antibiotics are often over-prescribed. The causes of diarrhea may be infective or non-infective. However, the reality stick around that almost in all of the cases are recovered easily and require only adequate rehydration. In all doubtful cases, an examination of stool should be done for cyst, ova and blood. Stool culture can be done in the presence of severe and/or bloody diarrhea, fever and systemic toxicity. Indications for antimicrobial therapy in diarrheal diseases must include patients with high fever, bloody diarrhea, severe dehydration, and systemic toxicity, extremes of age, history of recent antibiotic use, recent travel, and outbreak of food poisoning in the community. (De Bruyn G . et al, 2000).

3.2.4. The Most Prevalent Misuse Of Antibiotics:

There are some situations in which the use of antibiotics is clearly inappropriate. Below are some of the typical scenarios in which they are contraindicated:

1. Long term empiric therapy without clear evidence of infection: It is considered as one of the most common mistakes to give antibiotics when a patient does not appear to be responding to therapy.

2. Giving antibiotics to positive culture patient in the absence of disease: Correct principle of treatment in these situations involves obtaining cultures from the sites of infections only and avoiding treatment of a positive result of culture when signs and symptoms of active infection are absent, such as urinary tract colonization in old-age women.

3. Identification of causative organism but failure to narrow antimicrobial therapy: Almost of clinicians start with empiric therapy which is based on broad-spectrum agents until culture result is determined. When culture and susceptibility data are available, an antibiotic with the narrowest spectrum should be selected for

continuation of therapy, but this does not occur, especially, when the patient has good outcomes during taking empiric therapy.

4. Unnecessary prolonged prophylactic therapy: Antimicrobial agents can be used to prevent or avoid the occurrence of infection. For example, unnecessary prolonged pre-surgical antimicrobial therapy in most cases guidelines support for the use of a single, preoperative dose of an antimicrobial agent.

5. Frequent use of certain antimicrobial agents: The recurrent use of specific agents in a hospital or other health care setting can lead to development of resistant organisms to that particular antibiotic. For instance, the excessive use of fluoroquinolones over the past decade is thought to be, in part, responsible for the epidemic of a fluoroquinolone resistant strain of C difficile, the most common cause of nosocomial infectious diarrhea.

3.2.5. The Consequences Of Irrational Use Of Antibiotics:

1- Bacterial Resistance

The resistance is defined as "the acquired ability of bacteria to survive in the presence of concentrations of a chemical which are normally lethal". (Baquero, 2003). Antibiotic resistance can be acquired or intrinsic.

- Intrinsic resistance: It is due to the inherent structure or bacterial physiology.

i.e. resistance to penicillin due to lack of correct binding proteins and anaerobic resistance of bacteria against amino glycosides because taking up of the antimicrobial into the bacteria is oxygen dependant. (WHO fact sheet, revised 2002).

- Acquired resistance: It is the development of mechanisms by bacteria that prevent previously effective antibiotics from working. They include inactivation of the drug, reduce drug permeability to the bacterial cell wall, and target changes so that the drug will no longer bind to the bacteria and the bacteria will fail to metabolize the drug to its active form. Acquired resistance can develop by genetic mutation. (Morley PS. et al, 2005).

2- Human Toxicity

Although the antibiotics were designed to affect the physiology of microorganisms more than humans, these agents may have direct toxicity on patients. Sometimes this is considered as an extension of the mechanism of action of those agents when selectivity for microorganisms is not perfect and some of these toxicities may be dose related and can be prevented by dose reduction. This often occurs when doses are not adjusted properly and thus accumulate to a toxic level. (WHO, 1977).

3- Economic Cost

There are differences between countries in the price of drugs, which is more linked to individual drug products than to drug groups. (T.P.G.M. de vries, 1994). Over-use or incorrect use of antibiotics cause both patient and health care system to spend excessively on pharmaceuticals and this will be leading to waste of financial resources and the use of antibiotics inappropriately at early stage of disease may produce excess cost by increasing probability of prolonged disease and hospitalization. (Nausheen, S. et al, 2013). Also Antimicrobial resistance is increasing dramatically around the world in response to inappropriate antibiotic use and is causing significant morbidity and mortality It has been estimated that antimicrobial resistance costs annually $4000–5000 million in the USA and €9000 million in Europe. (Kathleen Holloway, 2011).

4- Antibiotic Allergy

The antibiotics can trigger immunologic reactions by forming a complexity with human proteins. The manifestations of these reactions may occur immediately such as anaphylaxis or hives or it may be delayed (rashes, serum sickness, drug fever).

The beta-lactam drugs are the most group of antibiotics for causing allergic reactions. It is difficult to determine that if a patient with an allergy to a particular antibiotic agent will have a similar reaction to another agent within that class. (Bertram G. Katzung, 2001).

5- Super infection

The human body is colonized by a various type of bacteria and fungi. These organisms are considered commensal, in that they benefit from living on or in the body but do not cause harm to the body and are known as normal flora. These normal floras compete with pathogenic organisms. When antibiotics are administered it will kill the commensal flora and pathogenic drug-resistant organisms can flourish because of the absence of competition. This is considered as super infection. (Goossens H. et al, 2007).

3.3. Strategies To Reduce An Antimicrobial Resistance (AMR):

According to WHO report which resulted in the meeting conducted on 19 December 2012, although many countries have good AMR surveillance, large number of gaps still remain. This monitoring process considered an area of AMR where success is possible, and where the global community can explain its obligation to move fore and look over a key part of this global issue. The implementation of effective policies and strategies to reduce AMR requires a good understanding of the prevalence of such resistance, and the factors that lead to its development and spreading. The most important need for AMR surveillance is that it increases our understanding of the distribution and extent of AMR, the level of the human disease and economic burden. (Dr Fukuda, 19 December 2012).

3.3.1. Guiding Principles For Combating The Emergence And Spread Of Bacterial Resistance To Antibiotics:

- Reducing inappropriate use of antibiotics in healthcare system because development of bacterial drug resistance, lead to loss of efficacy of existing antibiotics.
- Determination and control of antibiotic resistance requires the adoption of a “One-Health” approach to disease surveillance which recognizes that resistance can emerge in both humans and animals.
- An evidence-based infection control practice can be implemented to prevent the spread of resistant pathogens.

- It is necessary to accelerate private sector roles in the development of therapeutics to treat bacterial infections because current private sector interest in antibiotic development is limited.
- Bacterial resistance to antibiotics is a global health problem that requires international attention and collaboration, because bacteria do not recognize borders. (Edward A Belongia. et al, September 1998).

3.3.2. There Are 12 Steps To Prevent Antimicrobial Resistance:

The following steps were developed by(Kristin Brinsley. et al, October 2003).

Step 1. Vaccinate staff and patients

• Give influenza vaccine to patient at risk before discharge.

• Give the patient a pneumococcal vaccine in addition to routine vaccines (e.g. hepatitis B).

Step 2. Remove the catheter from the patient

• Employ catheters only when essential.

• Put the correct catheters.

• Remove catheters when they are no longer essential.

• Use proper insertion and catheter care protocols.

Step 3. Target the pathogen

• Obtain appropriate cultures.

• Determine appropriate empiric therapy to probable microbe.

• Use critical or definitive therapy to known pathogens and antimicrobial susceptibility results.

• Optimize timing, regimen, dose, route, and duration.

Step 4. Access the experts

• Consult the appropriate expert about patient with serious infections.

Step 5. Practice antimicrobial control

• Engage in local antimicrobial use quality improvement effort.

Step 6. Use local data

• Know your local antibiogram.

• Know your patient population.

• Obtain prior results of microbiology lab when patients transmit to your facility.

Step 7. Treat infection, not contamination

- Utilize suitable antisepsis for layout blood cultures.
- Culture the blood, not the skin or catheter hub.
- Use proper method to obtain and process all cultures.

Step 8. Treat Infection, Not colonization

- Do not treat the tracheal aspirate but treat pneumonia.
- Do not treat the catheter tip or hub but treat bacteremia.
- provide treatment for urinary tract infection, not the indwelling catheter.

Step 9. Understand when to say "No" to Vanco

- Treat infection, not contaminants or colonization.
- Treat fever in a patient with an intravenous catheter, but it is not a routine indication for vancomycin.

Step 10. Stop antimicrobial treatment

- When infection is treated.
- When infection is not diagnosed.
- When cultures are negative and infection is unlikely.

Step 11. Isolate the pathogen

- Use standard infection control precautions.
- Use approved airborne/droplet/contact isolation precautions.
- When in doubt, consult infection control experts.

Step 12. Contain your contagion

- stay home when you are sick.
- keep your hands clean.

3.4. Strategies To Reduce Inappropriate Use Of Antibiotic:

1. Strategies for providers or prescribers

Large numbers of physicians worldwide are aware that antibiotic resistance is an emerging problem which resulted from misuse or overuse of antibiotics. That means, providing information or education alone will be insufficient to change their prescribing behavior, so it is very important to overcome barriers to get more judicious prescribing by developing materials that support and change the implementation of effective techniques in the healthcare organizations. (Spellberg B. et al, 2008).

The most important elements include evidence based recommendations for diagnosis and treatment backed by professional societies, information to facilitate provider -patient communication and materials for patient education. (Edward A Belongia.et al, 1998).

Clinical practice guidelines must be developed and supported by other educational activities, such as multifaceted interventions which are more effective than single interventions. Printed materials have little effect on doctors' behavior when compared with other strategies. There are large numbers of studies showing that education at an individual or small group level and peer education are effective ways to change doctors' antibiotic prescribing behavior. Peer education effectiveness is increased when the message is delivered by local opinion leaders and is made relevant to the doctor's own practice. The implementation process of peer education on a broad scale may be difficult and expensive because of the need to identify, train, and support sufficient educators that alternative ways can be used like video presentation of information and although costs would be reduced, the ability to make discussion to each clinician's needs would be lost. (Ross- Degnan D. et al, 1997).

There is another successful technique to improve prescribing behaviors of doctors by using an internet to provide feedback to clinicians concerning their own prescribing of antibiotics practices. Computer assisted decision support is considered as a new communication technology that enhances the potential to practice guidelines and provide feedback to clinicians and it is used effectively to improve antibiotic prescribing in hospitals and could be extended to outpatient settings. (Isenalumhe AE. et al, 1998).

Materials Available For Prescriber To Support An Intervention Program On Antibiotic Use:

- Judicious antibiotic use principles for pediatrics and geriatrics infections.
- Providing academic sheets with one page summaries of the principles of antibiotic use.
- Question and answer sheets for viral respiratory diagnoses.

- A “prescription pad” including recommendations for symptomatic treatment for patients with viral respiratory infections.
- A letter to childcare providers announcing that the kid is able to return to the care day without an antibiotic.

2. Strategies for patients and the public

The most vital approach that is needed to increase the public's understanding of antibiotic resistance and to change expectations about use of antibiotics is multifaceted approach.

The most important elements should include

1- Implementing or conducting a campaign which is related to the public with driven advertising is an effective but expensive strategy to change behavior of health.

2- Fit out public educations regarding the variations between bacterial and viral infections. The potential prohibition of antibiotics taking is more complex than other health education messages because the risk of benefit ratio is less clear.

3- Interventions for patients at outpatient clinics must be an important component of a public education campaign. (Edward A Belongia.et al, 1998).

To ensure that messages about appropriate antibiotic use are emphasized it is important to provide effective educational materials to the communities. (Ross- Degnan D. et al, 1997). Below are some examples on these materials:

- Diffusion of relevant video shows
- Broadcasting and production of radio & TV material, including weekly bulletins, radio programs and micro shows.
- Dissemination of validated messages by posters, panels and presentation easels, pamphlets for patients’ education.
- Making interviews with journalists, and other key persons who can influence dissemination of information.
- Implementing of educational workshops with mothers and families.

- Organization of health fairs and workshops in places where there are gathering of people, like schools -- etc.

3.5. Antibiotic Stewardship Program:

It can be defined as a system of informatics, data collection, personnel, and procedures that encourages the best choosing, dosing, and duration of therapy for antimicrobial agents throughout the course of their use.

By implementing such program we can decrease inappropriate and excessive use of antibiotics, optimize therapy and clinical outcomes for the individual infected patient. (CDC, Centre For Disease Control And Prevention, 2014).

3.5.1. Interventions Involved In Antibiotics Stewardship Program In The Hospitals Care Facility:

Antibiotics stewardship interventions are recorded below in three categories such as, broad interventions, pharmacy-driven interventions, infection and syndrome specific interventions.

1. Broad interventions

• **Antibiotic "Time outs."** Almost all physicians start by using empirical therapy of antibiotics in hospitalized patients while diagnostic information is being obtained but clinicians often do not revisit the selection of the antibiotic after getting an enough laboratory data which includes culture results. Using antibiotic "time out" protocol provide a continuing review of the choice and need of antibiotics when the clinical picture is clearer and more diagnostic information is available. (Dellinger RP. et al, Feb 2014). The antibiotic therapy must be reviewed by clinicians 48 hours after antibiotics are initiated to answer these key questions:

1- Does this patient have an infection that will respond to antibiotics? If so,

2- Is the patient on the right antibiotic(s), dose, and route of administration?

3- Can a more targeted antibiotic be utilized to combat the infection?

4- How long should the patient receive the antibiotic(s)?

• **Prior authorization:** There are some facilities restricting the use of certain antibiotics based on the spectrum of activity, cost, or related toxicities to make sure

that the use of these agents is reviewed with an expert before therapy is initiated. This intervention demands expertise availability in antibacterial use and infectious diseases. Also authorization requires to be completed in a timely manner. (Fridkin SK. et al, 2014).

2. Pharmacy-driven Interventions

The following intervention was developed by(Stach LM. et al, 2012).

- **Changes from intravenous to oral antibiotic therapy automatically:**

  This must be done in appropriate situations and for antibiotics with good absorption (e.g., fluoroquinolones, trimethoprim, etc.), that will improve patient safety by reducing the need for intravenous access.

- **Adjustment of the dose:** This is in cases of organ dysfunction (e.g. renal adjustment).
- **Optimization of the dose:** For instance, dose adjustments depend on monitoring drug therapy, making the best therapy for highly drug-resistant bacteria, achieving the penetration of CNS, prolonged-infusion administration of some antibiotics, etc.
- **Time-sensitive automatic stop orders:** That is used for specified antibiotic prescriptions, especially antibiotics administered for surgical prophylaxis.
- **Prevention and find drug-drug interactions that is related to antibiotic usage:** To illustrate, interactions between some orally administered fluoroquinolones and certain vitamins.

3. Infection and syndrome specific interventions

The interventions which developed by (Sick AC. et al, 2013) are meant to get better prescribing for particular syndromes:

- **Community-acquired pneumonia:** The interventions which are taken for community-acquired pneumonia have focused on correcting problems in therapy, for example improving diagnostic accuracy, prescribing of therapy based on culture results and optimizing the duration of treatment to ensure guidelines acquiescence.

- **Infections of the urinary system:** Interventions for UTIs focus on avoiding unnecessary cultures of urine for asymptomatic patients and ensures that patients receive an appropriate therapy based on their susceptibilities and for the suitable duration.

- **Skin and soft tissue infections:** This intervention has focused on ensuring that patients do not get antibiotics with broad spectrum and ensuring the correct duration of treatment.
- **Clostridium difficile infections:** Guidelines for CDI urge providers to stop unnecessary antibiotics in all CDI diagnosed patients. However, this does not often occur. By reviewing antibiotics in newly diagnosed patients, this can recognize the best chance to stop unnecessary antibiotics and improve the clinical response of organism to therapy and decrease the risk of repetition.
- **Treatment of culture proven invasive infections :** An infection of blood stream is the best example on invasive infection that present good opportunities for interventions to improve the usage of antibiotic as it is readily fixed from the results.

3.6. Studies Were Done On Prevalence Survey Of Infectious Disease And Antibiotics Usage Rate:

Nearly in all European union countries, the healthcare-associated infections (HAIs) and antimicrobial resistance are viewed as the principle general health impendence. The European Centre for Disease Prevention and Control (ECDC) suggested in 2008 that the total aggregate weight of HAIs should be measured in routine and in an integrated way through the European Union.

The starting steps towards standardization of HAIs monitoring in Europe had been conducted on infections in intensive care units and surgical site infections by the 'Hospitals in Europe Link for Infection Control through Surveillance (HELICS)' project, from 2000 to 2003.

In this way, HELICS carried out standardized HAIs surveillance in 2004 and 2005, and later as portion of the 'Enhancing Patient Safety in Europe (IPSE)' network from 2005 to 2008, which was moved to ECDC in July 2008. Constant

observation, particularly prospective active monitoring, is the highest quality level. (UN general accounting office, 2004). In any case, repeated prevalence surveys (PPSs) explain more possible options for hospital-wide surveillance of all HAIs, but permitting the estimation of burden of disease by HAIs in acute hospitals, and prioritize regions still requesting interventions. (Stephen Morrissy. et al, 2015).

In the study completed by the European Centre for Disease Prevention and Control on healthcare-associated infections (HAIs) and antimicrobial use in European acute care hospitals, PPS was directed in January 2010 and the variables were gathered at hospital, patient and national level in 66 hospitals from 23 nations. A unit and patient based protocol were provided. Also questionnaires were utilized to evaluate feasibility. Of 19,888 reviewed patients, 7.1% had an HAI and 34.6% were accepting no less than one antibiotic. Results of prevalence were the highest in intensive care units, with 28.1% patients with HAI, and 61.4% patients with antimicrobial use. 1.8–2.2% of patients with pneumonia and other lower respiratory tract infections explain the most prevalent sort (25.7%) of HAI. Surgical prophylaxis was the sign of 17.3% of utilized antimicrobials and surpassed one day in 60.7% of cases. This PS study demonstrated that the point of assessing the burden of HAIs and antimicrobial use in European acute care hospitals was sensible and independent on the protocol utilized. (P zarb. et al, 15 May 2012).

In a study carried out by (Yilmaz et al, 2009), there were 153 patients (36.2%) receiving one or more antibacterial agents. (41.8%) of antibiotic therapy was for definitive indication and (58.2%) was given for prophylaxis purpose. Usage of antibiotics was appropriate for either treatment or prophylaxis in (45.7%), while it was inappropriate in the remaining (54.3%) patients. The most common inappropriate use of antibiotics was in surgical clinics (62.7%).

Another study was conducted in Turkey by (Ertugrul et al, 2009). 38 (54.3%) of the hospitalized patients was receiving antibiotics. At the end of the study, it was found that 12 (32%) of the patients who were on antibiotic use was receiving the agents in appropriate pattern. The most prevalent cause of inappropriate usage was due to prolonged use of prophylactic antibiotics (50%). Cefazolin (60%) and ampicillin/ sulbactam (21%) were the most commonly

prescribed antibiotics. The overall cost of antibiotics used on the day of study was 955.46 TL (13.65 TL per patient) and 327.98 TL of this (4.68 TL per patient) was due to inappropriate use.

Another study that was carried out in Turkey was planned to evaluate antibiotic utilization of inpatients treated in Gulhane Military Medical Academy, which has a 1,200-bed limit. On April 20, 2012, this study found out that prevalence of inappropriate antibiotic use changes between 19.0% and 72.4% and was 44.3%. That means that almost 50% of antibiotic treatment is inappropriate even in this hospital with such a relatively low use rate. When reasons for improper utilization are evaluated, they comprise of prolonged unnecessarily prophylaxis use and empirical applications. Additionally this study demonstrated that the rate of an antibiotic use rate was 39.7%. This moderately low rate of antibiotic use might be imputing to the efficient efforts of the antibiotics control committee of that hospital and the consultation provided by infectious disease specialists. (Hanfi Cem Gul. et al, 2013).

A cross-sectional study was conducted in a major tertiary hospital in Istanbul by (Asuman İnan et al, 2011). They found out that antibiotics were prescribed for (35.6%) of total inpatients. The empirical antibiotic use was more common (49.7%) than prophylactic (29.1%) and definitive therapy (21.2%). The antibiotics were used inappropriately in 44 patients (22.1%).The inappropriate usage was more common in prophylactic therapy (46.5%). The total daily cost of antibiotic therapy in this hospital was $3350.6 while the total cost of one day for hospital infection was $2137.1.

A prevalence study was performed in Vietnamese hospitals by (Thu et al, 2008) reported that 5,104 of 7,571 patients (67.4%) were taking antibiotics. The rate of antibiotics use was the highest in surgical specialty (93.2%) and the lowest in medical speciality (48.2%). The most commonly prescribed agents were from cephalosporin group (70.2%), penicillin (21.6%). The most common cause for inappropriate use were detected at surgical wards and gynecology departments. Approximately (1,573 of 5,104) of patients on antibiotics had an inappropriate indication.

A study performed by (Latour et al, 2012), showed that antibiotics utilized by 1,966 patients regarded as a part of 323 various facilities in 21 European nations were dissected. The majority of information acquired originated from the web-based ESAC (European Surveillance of Antimicrobial Cosumption). It was found out that the reason for antibiotic use was empirical in 54.4% of cases and prophylactic in 28.8% of cases and the significant variations between countries were found in terms of cause of antibiotic use. This study decided uroprophylaxis to be the most widely recognized cause, in spite of the fact that distinctions exist between countries.

A study was conducted in Benin by (Théodora AA et al, 2014) noted that the total surveyed inpatients were 3130, 597 of which with 972 nosocomial infections. The overall prevalence of hospital infections was (19.1%). The most frequent infections were related to the urinary tract (48.2%) and resistance pattern was detected in vancomycin resistance among enterococci (67.5%), methicillin-resistance (52.5%) among Staphylococcus aureus.

3.METHODOLOGY OF THE STUDY

3.1. Materials And Methods:

The study was conducted by reviewing electronic records of hospitalized patients, informal interviews of treating clinicians and patients and scanning of laboratory records.

3.2. Study Design:

This is an observational, cross-sectional survey of Antibiotic usage and health care associated infections for 8 days of April 2016.

3.3. Site Of The Study:

This study was carried out in surgical, medical, pediatrics and ICU wards at Near East University hospital. The medical ward includes Internal medicine, geriatrics, gynecology, Infectious disease, respiratory and allergy, cardiology, GIT, orthopedic and urology departments. This is tertiary teaching care hospital and one of the largest leading medical facilities in the private sector in Lefkosa, Northern Cyprus. This hospital has a 55,000 square-meter closed area with 209 private single patient rooms, 30-bed Intensive Care Unit, 8 operating theatres, 17-bed Neonatal Intensive Care Unit.

3.4. Sampling And Time Window:

Period prevalence survey of randomly selected inpatient were conducted between 11 and 18 of April 2016 at Near East tertiary hospital. To ensure feasibility of the survey one week was allowed to complete gathering of desired data.

3.5. Inclusion Criteria:

All hospitalized patients of any age were eligible for inclusion and also patients were temporarily absent from the wards (e.g. for endoscopy, surgery, medical imaging) were included while patients in outpatient area (including haemodialysis patients) and psychiatric, neurology, oncology, ophthalmology,

ENT, rehabilitation and emergency units were excluded. Only antibiotics that used systemically were included in this study while topical antibiotics was excluded.

3.6. Data Collection:

Some of the necessary data was taken from computerized records during the study and the rest of the data was gathered by reviewing the patients records at each clinic. Demographic information for the patient was included in the first part of the survey like gender, age, name of the ward where the patient was treated, date of hospital admission while the second part included information about antibiotics for example, antibiotic usage indication, generic name of antimicrobial agent used, date of start using antibiotic, dose frequency, rout of administration, dosage form. Also laboratory and culture results were gathered to determine if antibiotics were used for empirical, prophylaxis or definitive therapy. The last part was about HAIs which include data on microorganisms and only results that available on the time of the survey were included. Age of the patient, date of hospital admission, date of starting antibiotics and length of hospital stay, were used to estimate the total number of health care associated infection.

3.7. Case Definitions :

Case definitions that were developed by the United States Centers for Disease Control and Prevention (CDC) were used. We considered that an active infection was **healthcare-associated infection** (associated to acute care hospital stay only) when it meets the following criteria:

1-If the signs and symptoms started on day 3 of the current admission or later (with day 1 the day of admission) and it was not present or incubating at the time of admission.

2-Antibiotics treatment was continuous on the day of the survey.

The HAI was classified as lower respiratory tract infection, surgical wound, urinary tract infection, skin and soft-tissue infections, bloodstream, catheter related infection and others.

An antibiotic appropriateness was estimated by using the Council for Appropriate and Rational Antibiotic Therapy (CARAT) criteria (Slama TG et al,2005). These criteria included requirements to rationalize the use of antibiotics such as

evidence-based results, therapeutic benefits, optimal drug, optimal duration, safety and cost-effectiveness. The CDC guidelines for antimicrobial use were also used as references for the appropriate therapeutic recommendations and the cost of antibiotic therapy was calculated in United States dollars.

3.8. Data Analysis:

Privacy of patients was provided by coding. All data were analyzed using the Statistical Package for Social Sciences software (SPSS version 22). The data were described using frequency distribution. Categorical variables were analyzed by Chi-square test and statistical significance was accepted when the chance for confidence was less than 1%.

4. RESULT

On the time of prevalence study, the total number of hospitalized patients was 137. The percentage of patients on surgery, medical, pediatric and ICU wards were 23(16.8%), 86(62.8%), 16(11.7%), 12(8.8%), respectively.

4.1. Antibiotic Use:

Of 137 inpatients, 54 (39.4%) were on one or two antibiotics. Among patients receiving antibiotics, 7 were on surgery ward, 35 were on medical ward, 6 on pediatric ward and 6 on ICU unit. The prevalence of antibiotic use according to specialty, gender are summarized in table 1. We do not find a significant difference between antibiotic use and specialty (P = 0.7) and gender (p = 0.9).

Table (1). Prevalence Of Antibiotic Use By Specialty And Gender.

	Total survey patient		**Patient on antibiotic use**	
Speciality	**N**	**%**	**N**	**%**
Surgery	**23**	**16.7**	**7**	**30.4**
Medicine	**86**	**62.7**	**35**	**40.7**
Pediatric	**16**	**11.6**	**6**	**37.5**
ICU	**12**	**8.7**	**6**	**50.0**
Total	**137**	**100**	**54**	**39.4**
Gender				
Male	**69**	**50.3**	**27**	**39.1**
Female	**68**	**50.3**	**27**	**39.1**
Total	**137**	**100**	**54**	**39.4**
	Shown by row percentage			

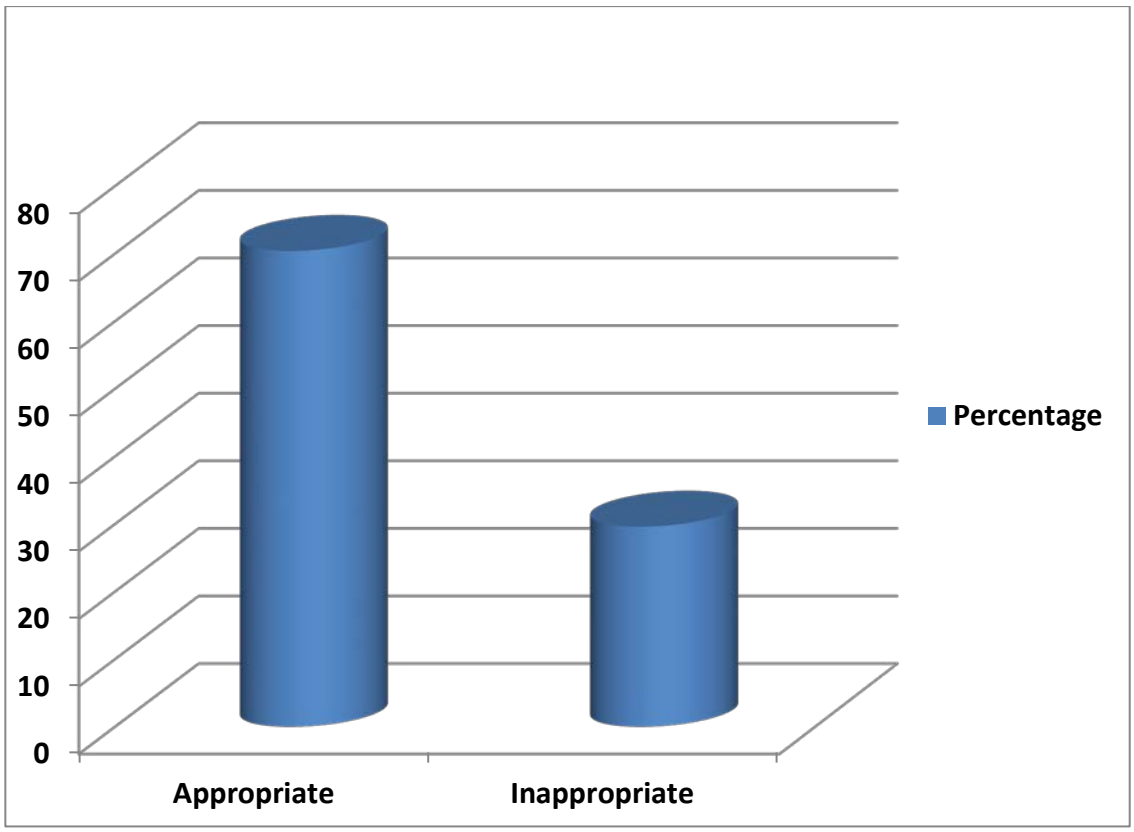
Of patients on antibiotics, 49(90.7%) were using one antibiotic, and 5(9.2%) were using two antibiotics. The indication of using antibiotic were evaluated by using criteria of empirical, prophylaxis and definitive therapy. It was found out that the most common indication of using antibiotics was empirical (57.4%) while (24.1%) and (18.5%) were prophylaxis and definitive therapy respectively. The appropriateness of antibiotic use according to specialty and indication are given in table 2.

Table (2). Appropriateness Of Antibiotic Use According To Specialty And Indication.

	Appropriateness		**Inappropriateness**		**Total**	
Specialty	**N**	**%**	**N**	**%**	**N**	**%**
Surgery	**7**	**100**	**0**	**0**	**7**	**100**
Medicine	**22**	**62.8**	**13**	**37.1**	**35**	**100**
Pediatric	**4**	**66.7**	**2**	**33.3**	**6**	**100**
ICU	**5**	**83.3**	**1**	**16.7**	**6**	**100**
Total	**38**	**70.4**	**16**	**29.6**	**54**	**100**
Indication						
Empiric	**25**	**80.6**	**6**	**19.4**	**31**	**100**
Prophylaxis	**9**	**69.2**	**4**	**30.8**	**13**	**100**
Definitive	**4**	**40.0**	**6**	**60.0**	**10**	**100**
Total	**38**	**70.4**	**16**	**29.6**	**54**	**100**
	Shown by row percentage					

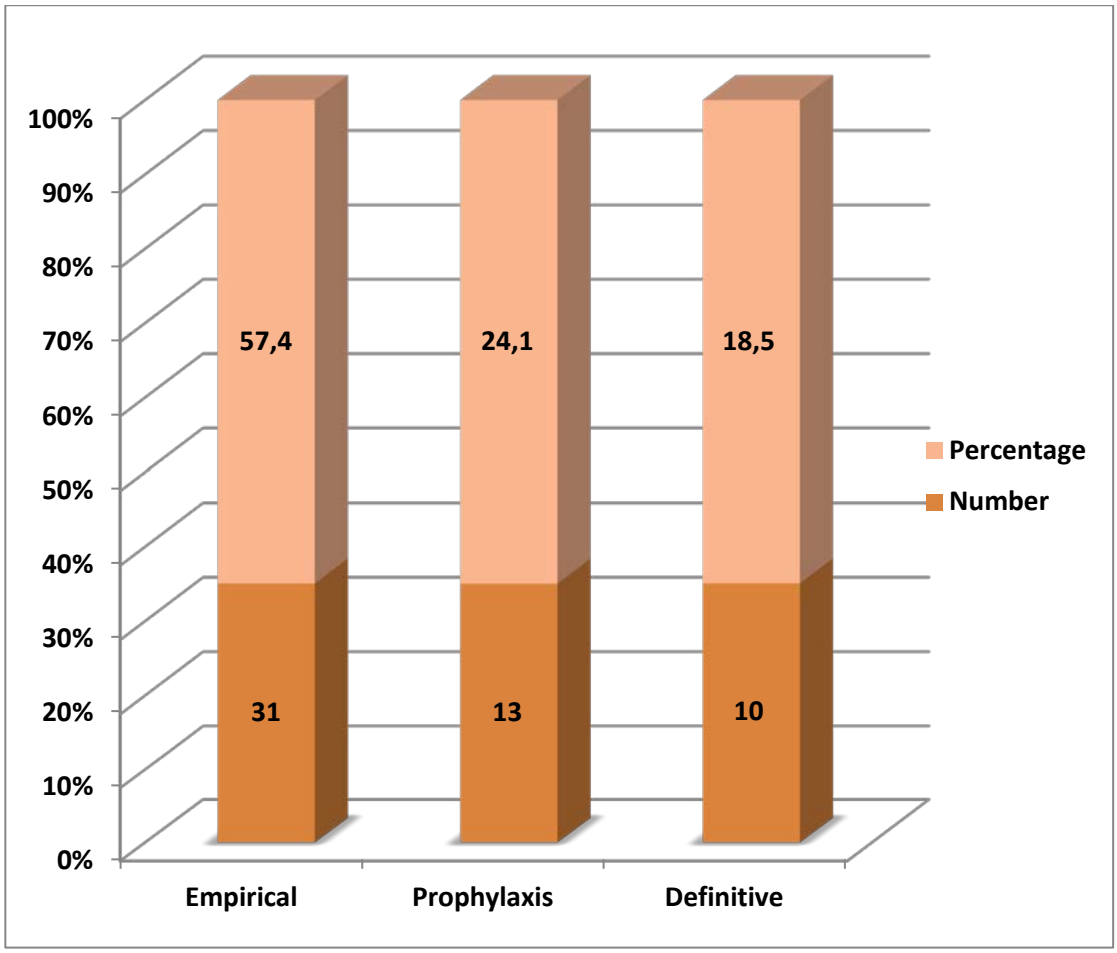
At the time of analyzing the Appropriate use of antibiotic according to indication, it was found that, the most common appropriate use was for empirical (80.6%) and prophylaxis (69.2%), while the most common reason why antibiotic were used inappropriately was for definitive therapy (60.0%) and prophylaxis (30.8%).

Fig. No (3) Rationality Of Antibiotics



*Appropriate usage of antibiotics (70.4%) was significantly (P<0.01) higher than inappropriate usage (29.6%).

Fig. No (4) Indications Of Antibiotics



*It was observed that empirical therapy was significantly higher than prophylaxis ($P < 0.01$).

Antibiotic was given by two routs, intravenous (88.9%) and oral rout (11.1%). On the study period, 59 antibiotics were used by 54 hospitalized patients. The distribution of antibiotics by group is summarized in table (3).

Table (3). Distribution Of Antibiotics By Groups.

Antibiotics	**N**	**%**
Cephalosporin	29	49.2
Cefazoline	17	
Cefuroxime	3	
Ceftriaxone	8	
Cefexime	1	
Betalactam+Betalactamase inhibitors	13	22.0
Augmentine	6	
Tazoper	5	
Ampicilline	2	
Macrolide Clarythromcine	2	3.4
Carbapenem Moperopenem	1	1.7
Quinolones ciprofolxacine Lefofloxare	8 7 1	13.6
Rifampine	3	5.1
Snlfonamide+Trimetoprim	1	1.7
Daptomycine	2	3.4
Total	59	100

Based on the group, the most commonly used antibiotic was cephalosporin, 29 (49.2%) and according to the preparation , the commonly prescribed antibiotics were cfazoline17, ceftriaxone 8, Augmentine 6 and Tazoper 5. It was found out that, the most antibiotic used for prophylaxis and empiric belonged to cephalosporin group (92.3%). While the preferred antibiotic for definitive therapy was from Betalactam group (23.1%).

Table (4). Type Of Infections For Which Antibiotics Was Prescribed.

Type of infections	N	%
Upper respiratory tract infection	5	12.8
Lower respiratory tract infection	5	12.8
Blood stream infections	4	10.3
Urinary tract infections	13	33.3
Skin and soft tissue infection	1	2.6
Prosthesis	1	2.6
Meningitis	2	5.1
Appendicitis	1	2.6
Others	9	21.9
Total	41	100

The above table explains types of clinical diagnosis for 41 patients on the period of study. Of those 41 patients, 15 had hospital acquired infections. The most prevalent infections was urinary tract infections 5 (33.3%).

The overall cost of antibiotic therapy in one day in the centre of study was ($919.61) and the mean daily cost per patient was ($17.02). The mean daily cost per patient was ($ 8.12) in surgical wards, ($21.57) in medical wards, ($ 6.94) in pediatrics and ($5.79) in ICU ward.

4.2. Hospital Acquired Infections:

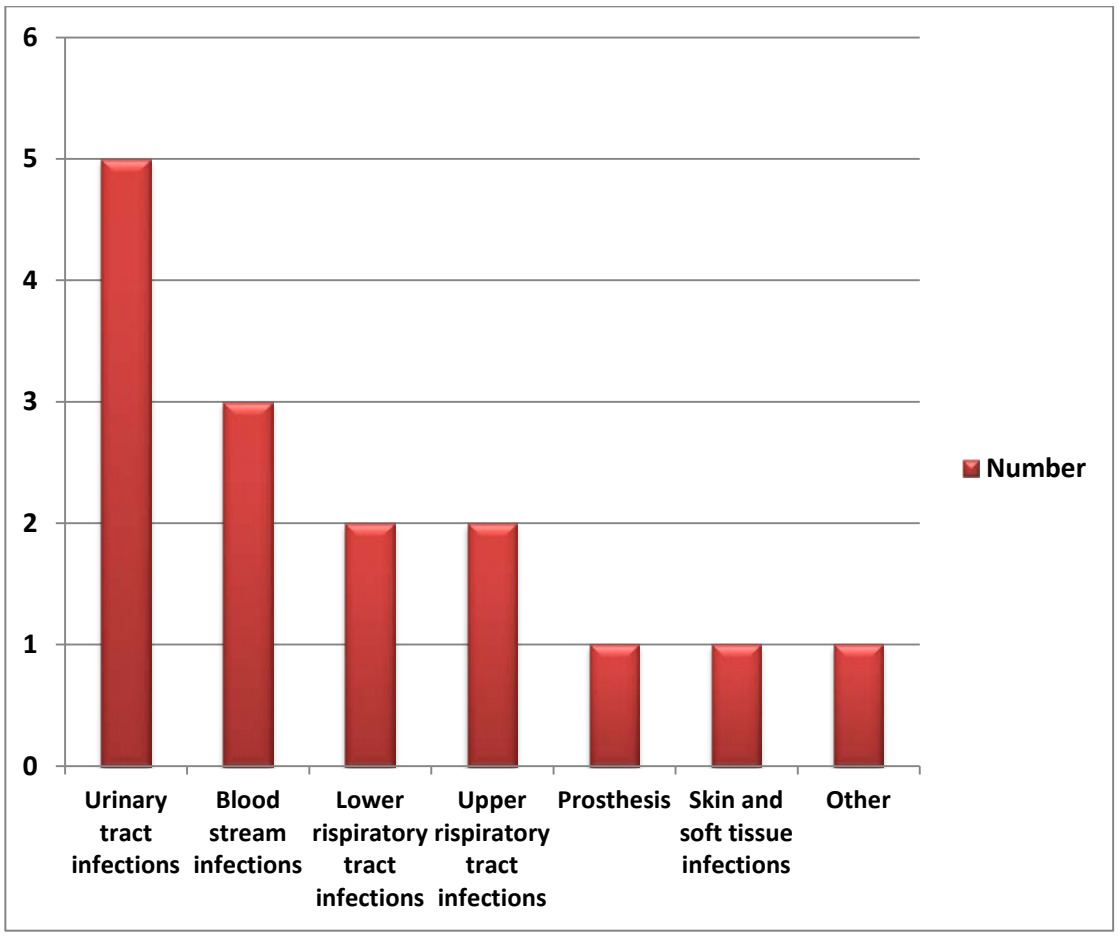
The overall, 15(10.9%) of hospitalized patients with hospital acquired infections, ranged from 11 (12.8%) in medical to 4 (33%) in intensive care unit. The prevalence of hospital acquired infection by age group and length of hospital stay is summarized in table 4.

Table (5). Prevalence Of HAIs By Gender, Age Groups And Length Of Hospital Stay.

		Total patients	HALs	%
$\rho = 0.1$	**Gender**			
	Male **Female**	**69** **68**	**10** **5**	**14.5** **7.4**
$\rho = 0.001$	**Age group***			
	< 30 years **>30 years**	**54** **83**	**0** **15**	**0** **18.7**
$\rho = 0.00$	**Length of hospital stay***			
	3 – 6 days **6 – 10 days** **>10 days**	**61** **49** **27**	**0** **0** **15**	**0** **0** **55.6**
	Total	**137**	**15**	**100**
	Shown by row percentage			

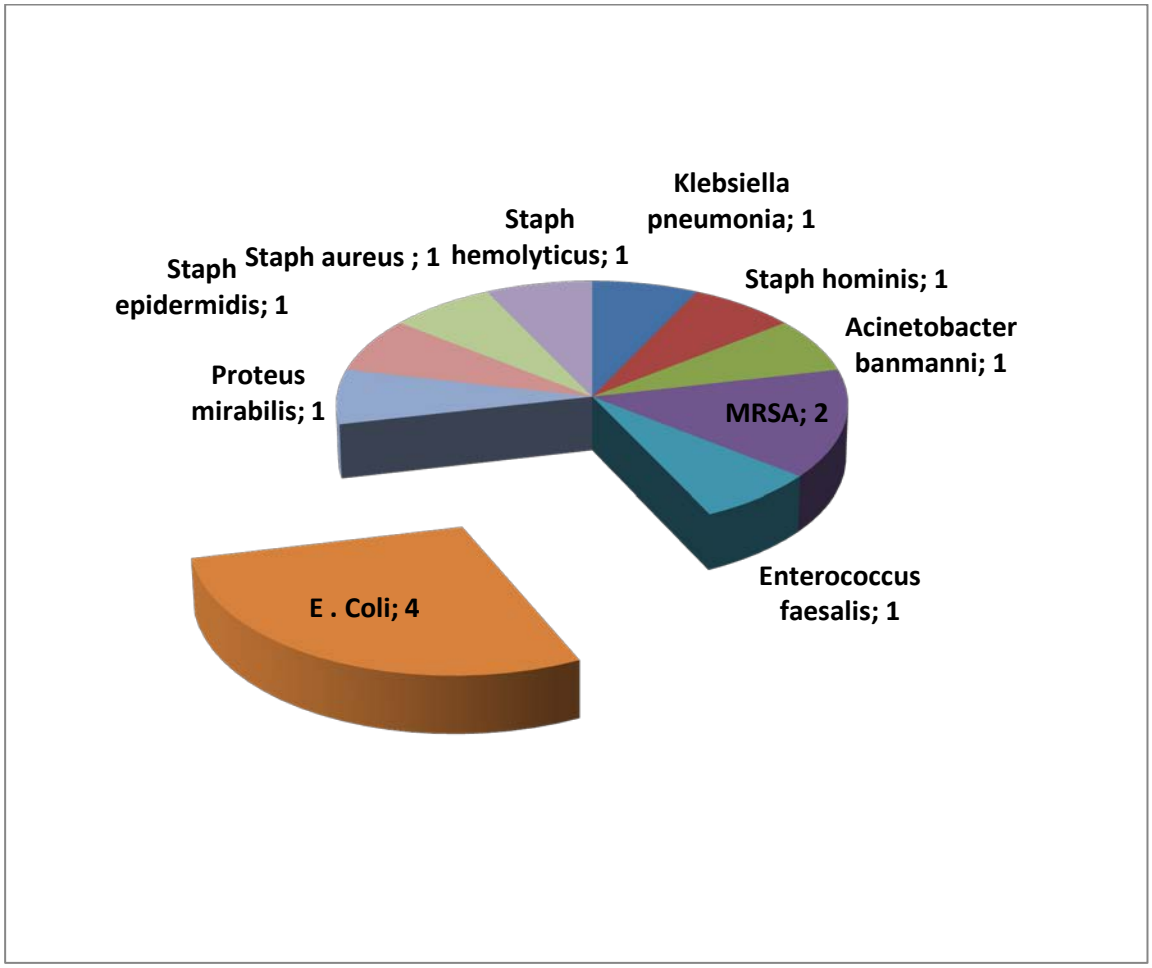
The two variables (age and hospital stay) were significantly related to HAIs (P<0.01). Patients aged above 30 years (PR:18.07% , P = 0.001)* and patients who had spent more than 10 days in the hospital since admission (PR :55.6% , P = 0.000)* were more likely to have hospital acquired infection compared to younger patients with shorter stay in the hospital. But we did not find any statistical significant regarding the relation between HAIs and gender (p = 0.1).

Fig. No (5) Type of hospital acquired infections



Urinary tract infections were the most prevalent infections among patients with hospital acquired infections.

Fig No.(6) Number Of Isolated Bacteria In Nosocomial Patients



From the above graph, it is observed that the most commonly isolated bacteria was E. coli (26.7%). The percentage of MARSA was (13.3%). The most prevalent isolated bacteria in patients with nosocomial infections was Staphylococcus species..

The total daily cost of nosocomial infections was ($ 482) and the mean daily cost per patients with hospital infections was ($32.13).

5. DISCUSSION

5.1. Antibiotics Use:

One of the most considerable roles to establish a good and cost-effective health care system is the appropriate use of antibiotics in the hospital.

Since our study center provides a service for approximately 40% of the population of Northern Cyprus , we believe that our results may be used to give a general view of the situation in Northern Cyprus hospitals.

The main purpose for using antibiotics are empirical, prophylaxis and definitive therapy.

According to the results of various prevalence studies performed in Turkey and worldwide by (Yilmaz et al), (Ertugrul et al), (Hanefi et al) and (Thu et al), antibiotics usage rate varied between (36.2%) to (67.4%). In our study (39.4%) of the inpatients were receiving antibiotics. It demonstrated that the antibiotic usage rate was relatively low.

In a similar way, the inappropriate usage rates in this study was (29.6%) and it is considered low when compared with the results that were reported in the previously mentioned studies that varied between (30.8%) to (68.8%).

There are worrying facts when comparing the percentage of antibiotics used inappropriately with the relatively low percentage of antibiotic usage in the hospital.

When assessing the cause of inappropriate use of antibiotics, they found out that the most common reasons why antibiotics were used inappropriately was unnecessary prolonged use of prophylaxis and empirical therapy while in this study (37.5%) of inappropriate usage was an improper choice of AST and (37.5%) was from prolonged empirical use of broad spectrum antibiotics without presence of clear diagnosis.

The antibiotics which were used by 6 patients with definitive the ropy may be prescribed with no consultation by infectious disease specialist for any of those patients and the agents which were used by these patients were not the same agents that would have been prescribed by a specialist at infections disease department.

In a study performed by(latour et al) antibiotics utilized by 1,966 patients regarded as a part of 323 various facilities in 21 European nations were dissected. The majority of information acquired originated from the web-based ESAC. It was found out that the reason for antibiotic use was empirical in (54.4%) of cases and prophylaxis in (28.8%) of the cases. Also our study determined empirical (80%) and prophylaxis (33%) to be the most prevalent cause of antibiotic use and it is relatively higher than the percentage in the above mentioned study.

In our study, it was observed that, the higher rate of empirical therapy was started without concomitant microbiological investigations.

One of the most important issue in any country is the cost. We detected that the overall one-day cost of antibiotic therapy in this hospital was ($ 919.61) while the mean daily cost of antibiotic per patient was ($17.02). Our finding was relatively higher than that in a study from Turkey performed by (Naz et al) which found out that the mean daily antibiotic cost per patient was ($13.8) while mean daily antibiotic cost for hospital infection was ($25). In fact, the accurate antibiotic therapy costs were affected by various factors. For example, excessive use of intravenous administration, monitoring antibiotic adverse effects, and nursing services. Thus, we suppose that the actual cost of antibiotic therapy is higher than the cost that was reported in these studies.

One considerable thing was observed in this study that high percentage of patients was on intravenous antibiotics therapy (88.9%) as compared to oral rout which is 3 times costly than oral dosage form.

5.2. Hospital Acquired Infection:

In our survey , we used CDC standardized definitions to record data on HAIs. The data of onset of infection was recorded in this survey to determine which infection could be classified as hospital acquired infection and according to that, it was possible to detect if the HAIs was created from long stay in the hospital.

The overall prevalence of HAIs reported in this study was (10.9%). Our result was considered in a medium range when compared with the results that ranged between (8%) to (19.1%) for studies that performed by (Pujate et al) and (Ider BE et al).

The most prevalent cause for HAIs was urinary tract infection (33.3%). It is relatively low when compared with the result of urinary tract infections (48.2%) in study performed by (Théodora, AA et al).

Prevalence of HAIs was high in patients aged over 30 years old and in those in hospital for longer than 10 days. We consider that elderly patients are more sensitive to HAIs. The most common prevalent type of bacteria that was isolated in patient with nosocomial infections was staphylococcus species. Our results were consistent with a finding in a study performed by (Rachid Razine et al).

The mean daily cost per patient for hospital infections was ($32.13) in our hospital. In a study conducted by (Asuman İnanrt et al) was (54.7%). Our finding was relatively low when compared with this study.

6.CONCLUSION AND RECOMMENDATIONS

6.1.Antibiotic Use:

- In the end, this survey showed that the rate of inappropriate antibiotic use in our hospital was low when compared with other studies. Antibiotic usage rates which were detected in this study was relatively low and this was may be due to the low number of total hospitalized patients. Definitive therapy is still a major problem, so infectious disease specialist agreement and implementing a restriction policy is efficient for appropriate use of antibiotics. Also widely use of broad spectrum antibiotics as empirical therapy without culture result to guide therapy was determined in this study.

- According to our finding, we recommend that it is considerable to review an antibiotics prescribing practice in the hospital to decrease the use of broad spectrum agent and subsequent prevention the of development of bacterial resistance to these agents and this will be optimized by providing an encouragement to a study design with an infectious disease specialists intervention and microbiological progression. This hospital should institute a formulary for antibiotic use and therapeutics committee of the hospital must define rules that prevent access to particular agents. We believe that implementing antibiotic stewardship program within the hospital will be effective to decrease inappropriate and excessive use of antibiotics, optimize therapy and clinical outcomes for the infected patient and also it is very important to provide education programs regarding the rational uses of antibiotics to all postgraduate student and antibiotic prescribers.

6.2. Hospital Acquired Infections:

- In conclusion, the prevalence of HAI was relatively high in the Near East University hospital as a private hospital and this type of infections are an important part of extra costs in the hospital.

- Our study provides requisite data for future surveillance of HAI and this type of study should be repeated at least two times annually. It pliable us to characterize

the patients profile who are at high risk of developing HAI. Therefore we suppose that they should focus on patients with longer length of stay. It is demanding to institute prevention programs at the hospital level to reduce burden of HAIs and then maybe it will be the first step to establish a national strategy in this trend. However, observational studies are in demand to provide more information regarding the incidence of HAI and related risk factors.

7. LIMITATIONS

This study has some limitations:

1- It was carried out in only one hospital, so we cannot generalize the results through- out Northern Cyprus .

2- It was conducted in April, when the number of patients receiving antibiotics could have been lower than in other periods of the year.

3- Information on the usage of invasive device was not collected, so we could not estimate the relation between using of invasive device and prevalence of nosocomial infections.

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