TURKISH REPUBLIC OF NORTH CYPRUS
NEAR EAST UNIVERSITY
HEALTH SCIENCES INSTITUTE

Antibiotics Utilization pattern in pediatric patients admitted to a tertiary hospital in North Cyprus

Nour AL Kharrat

MASTER THESIS

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

DEPARTMENT OF CLINICAL PHARMACY

Mentor

Assist. Prof. Dr. Abdikarim Abdi

2019 - Nicosia

TURKISH REPUBLIC OF NORTH CYPRUS
NEAR EAST UNIVERSITY
HEALTH SCIENCES INSTITUTE

Antibiotic utilization patterns in children admitted to a pediatric general medical ward in North Cyprus

By:
Nour AL Kharrat

Advisor:
Assist. Prof. Dr. Abdikarim Abdi

2019 - Nicosia

Approval

Thesis submitted to the Institute of Health Sciences of Near East University in partial fulfillment of the requirements for the degree of **Master of Science in Clinical Pharmacy.**

Thesis Committee:

Chair of the committee **Assoc. Prof. Dr. Bilgen Basgut**

Near East University

Sig: ……

Member: **Assoc. Prof. Dr. Emre Hamurtekin**

Sig: ……

Advisor: **Assist. Prof. Dr. Abdikarim Abdi**

Near East University

Sig: ……

Approved by: **Prof. Dr. Hüsnü Can BAŞER**

Director of Health Sciences Institute
Near East University

Sig: ……..

Acknowledgments

Special thanks to **my parents, Obadah**, **my sister, and my brothers** … nothing can be without you and your great support to me... You hold my hands in all steps and still standing by me … giving me every things I need and more... No words can describe how much you support and encourage me to do my best …

Osama... If I thank you it will be less than how much you gave me ... you always stand by me in all the hard times … help, support, and believe in me … deep thanks to you and to your parents …

Million thanks to my advisors **prof. Bilgen** and **prof. Abdi** … I will be proud for the rest of my life because you were my advisors … you gave me a lot of knowledge, Support, and encouragement … you were a second family … thanks from all my heart…

My **teachers** and **friends**... Thanks for your support … every word you said it to me was a great support...

Name of the student: Nour AL Kharrat
Mentor: Assist. Prof. Dr. Abdikarim Abdi
Department: Clinical pharmacy
Abstract

Introduction: Antibiotics have many advantages in treating infections, but at the same time it can be unnecessary, harmful or life threating if used in the wrong way. Antibiotic resistance can cause at least 2 million illnesses and 23000 deaths in U.S annually meanly because of the over or inappropriate use. In hospitals, up to 50% of antimicrobial use is inappropriate .pharmacists play an important role in prevention of antimicrobial resistance. It is important to give the rational drug therapy to the patients especially to the pediatrics.

Aim: The aim of the study is to assess usage of antibiotic in hospitalized children, and based on the findings recommend solutions and recommendations in an effort to appraise the rational use of antibiotics in pediatric wards. .

Method: A retrospective study of antibiotic utilization patterns in pediatrics between 1st September 2017 and 30th September 2018. Patients' information and data was obtained from patient archives and electronic records in Near East university hospital (NEUH). There were 332 pediatric patients admitted to NEUH during 1st September 2017 and 30th September 2018. 229 patients were using antibiotics and were included in the analysis. The rationality of Antibiotic prescriptions were analyzed using Infectious Diseases Society of America (IDSA), Centers for Disease Control and Prevention (CDC) guidelines , Up TO Date, world health organization (WHO) e-pocketbook guidelines. Also, The rationality of antibiotic prescriptions analyzed by a pharmacologist, clinical pharmacist and a researcher step by step looking to the drug selection, dose, rout of administration, duration of therapy, lab tests and cultures each case individually.

Result: Out of 332 patients, 229 cases (67%) were using antibiotics and were included in the analysis. Of them 107 (46.7%) were females and the rest 122 (53.3%) were males. In general 153 (66.8%) of the patients including newborns received antibiotics rationally while 76(33.2%) were identified as irrational. preterm newborns infections was the most commonly associated disease with an irrational antibiotic use practice ($p<001$) followed by Pneumonia ($p<001$). The most common identified problem was Missing culture 39(12.5%), followed by Irrational drug selection 30(9.6%) ($p<001$)

Conclusion: Children have unique medical needs related to antimicrobials and thus deserve focused efforts. We will be able to decrease irrational use of antibiotics by implementing the guidelines and translating it to our protocols. Strategies for more justified administration of antibiotics especially broad –spectrum ones are necessary.

Key Words: pediatrics- antimicrobial resistance- antibiotics –infections – stewardship program- Northern Cyprus

STATEMENT (DECLARATION)

Hereby I declare that this thesis study is my own study, I had no unethical behavior in all stages from planning of the thesis until writing thereof, I obtained all the information in this thesis in academic and ethical rules, I provided reference to all of the information and comments which could not be obtained by this thesis study and took these references into the reference list and had no behavior of breeching patent rights and copyright infringement during the study and writing of this thesis.

Nour AL Kharrat

CONTENTS

Figures

Tables

ABBREVIATIONS

ABBREVIATION	EXPLANATION
AMR	Antimicrobial resistance
US FDA	United States- Food And Drug Administration
WHO	World Health Organization
TBW	Total Body Weight
CNS	Central Nervous System
DDIs	Drug-Drug Interactions
GFR	Glomerular Filtration Rate
ICD 10	Classification of Diseases and Related Health Problems
GI	Gastrointestinal
UTI	Urinary tract infection
AST	Antimicrobial Susceptibility Testing
IV	Intra Venus
IM	Intra Muscular
PO	Orally
ASPs	Antibiotic Stewardship Programs
ADME	Absorption, Distribution, Metabolism, and Excretion
pH	Power of Hydrogen
SPSS	Statistical Package for the Social Sciences
NEU Hospital	Near East University Hospital
ICU	Intensive Care Unit

Classification of Diseases and Related Health Problems

J02	**Acute pharyngitis**
J03	**Acute tonsillitis**
J00	**Acute nasopharyngitis [common cold**
J01	**Acute sinusitis**
J20	**Acute bronchitis**
J21	**Acute bronchiolitis**
J00-J99	**Influenza and pneumonia**
J69.0	**Aspiration pneumonia NOS**
P24.	**Neonatal aspiration pneumonia**
J12	**Viral pneumonia**
J13	**Pneumonia due to Streptococcus pneumonia**
J14	**Pneumonia due to Hemophilus influenza**
J15	**Bacterial pneumonia**
K35	**Acute appendicitis**
A09	**Infectious gastroenteritis**
G00	**Bacterial meningitis**
J45.	**Asthma**
N39.0	**Urinary tract infection**
NOS (K52.9)	**gastroenteritis**
Z16-Z16	**Resistance to antimicrobial drugs**

1- INTRODUCTION:

Pediatric have special considerations in the pharmacotherapy treatment. We cannot deal with them as adults because they need unique care and they have different responses to medications. pediatric population distribute from premature neonates, who may be weighing less than a pound, to full-grown adolescents, who may very well weigh more than 200 pounds. So they have special issues like unique antimicrobial dosing needs and special drug monitoring (Kearns G. L.-R., 2003) (Bielicki, 2015).

Studies shows that the range of pediatrics in hospitals who receive at least one antibiotic is between 33 % and 78 % (Levy E. R., 2012) (Versporten, 2016). Moreover, antibiotics are prescribing in about 20 % of pediatric ambulatory visits (Hersh A. L., 2011). Unfortunately; most of these antibiotics are inappropriate or unnecessary. For example; some antibiotics are prescribing to children who have non-infectious diseases or viral infections (Nash, 2002) (Esposito, 2001). Also, in other cases, pediatrics who suffer from infections for which narrow-spectrum drugs are recommended are given broad-spectrum antibiotics (Hersh A. L., 2011) (McCaig L. F., 2003). Finally, a lot of pediatrics receive antibiotics prescriptions with a wrong daily dosage or for a longer duration (Levy E. R., 2012) (Nash, 2002) (Graham, 2006).

Among the drugs that most commonly given to pediatrics in hospitals and community pharmacies are Antibiotics (Gerber J. S., 2010) (Spyridis, 2016).

Antibiotics are effective drugs in the fight against bacterial infectious diseases. About 50 years ago, since their first appearance, antibiotics have saved millions of lives. (Radyowijati, 2003).

Antimicrobial resistance (AMR) occurs when microorganisms start to be able to resist the antibiotic that has been used to stop them (Resistance., 2015). Resistant microorganisms can continue growing or still alive in the presence of a concentration of antibiotic that is usually used to inhibit or kill non-resistant microorganisms of the same species. (Hazards, 2009).Failure of Treatment caused by AMR lead to: increased side effects; longer hospitalization; psychological problems because of the reduced quality of life; increased burden on families; and inadequate or delayed treatment which can sometimes cause death. (Besançon, 2016)

Drug utilization is important to examine the clinical and cost effectiveness of pharmacotherapy (Ceci, 2002). The World Health Organization (WHO) defined Drug utilization as ‘‘the marketing, distribution, prescription and use of drugs in a society, with special emphasis on the resulting medical, social and economic consequences’’ (Organization, 2003) . Thus, the aim of drug utilization research is to achieve the rational use of drugs, and provide evidence of prescribing patterns.

Most of the previous drug utilization studies on pediatrics are conducting to describe how some drugs or groups of drugs are using, for example, the prescribing trends with antimicrobials (Porta, 2012), or to evaluate the difference in practice with pediatrics from the adult dosing guidelines, recommendations in the summary of product characteristics, or hospital formularies (Neubert, 2008) (Star, 2011).
According to the World Health Organization, rational use of drugs means that the patient receives medications appropriate to his clinical needs, in the appropriate doses, for an adequate duration, and at the lowest cost (who, 1987)

In the first part of this thesis project, we provide general information about pediatric and their special therapy needs. The antibiotic use with pediatric will be discussed. Then, general concept of rational drug use and irrational drug use will be defined. We will present more details about the rational use of antibiotics especially with pediatrics and the consequences of irrational antibiotics use. The latest strategies and solutions to improve rational antibiotic use and the recommendations to implant stewardship program will be discussed.

In the second part of this project we present the assessment and utilization of antibiotics in pediatric in a tertiary teaching hospital in Northern Cyprus.
The aim of the study is to assess usage of antibiotic in hospitalized children, and based on the findings recommend solutions and recommendations in an effort to appraise the rational use of antibiotics in pediatric wards.

2. Background

2.1 Overview of pediatric patient care:

Pediatrics is a specialty that include the physical, psychosocial, developmental, and mental health for children with different ages. Pediatric care begins from delivery and continues through gestation, infancy, childhood and adolescence. (Hardin, 2017)

Many factors about pediatric should be considered in practice, because they have special needs and require unique health care. Age dependent pharmacokinetic characteristics, Body compartment sizes, Body composition, Protein concentration and function, Hepatic Elimination, Renal Elimination, Absorption, metabolic capacity, *Changing* weight and height, and ease of administration all should be taken into account to recommend suitable age groupings. (WHO, 2007)

2.1.1 Pediatric Populations:

There are different discussions applied in dividing the pediatric population by age, which based on developmental progression. In 2006, The British National Formulary for Children provides doses for neonates (under 1 month in age), then for children from 1 month to 4 years, and for children 4 year to 10 years (J, 2006). But many notations do not follow this age division. For example, the US FDA classification is: neonate (birth to 1 month), infant (1 month to 2 years), children (2 to 12 years) and adolescent (12 to < 17 years) (US FDA, 2013) and we use this division in our study.

Previously in 2003 the US FDA defined pediatric subpopulations as: neonate (birth to 1 month), infant (1 month to 2 years), children (2 to 12 years) and adolescent (12 to < 21 years) (FDA, 2003). They believed that this age range is suitable for the use of medical devices in pediatric subpopulations, but exceptions could be made when the pediatrician and family agree to an older age, particularly in the case of a child with special health care needs. (Hardin, 2017)

2.1.2 Considerations in Pediatric Therapeutics:

There are 4 important facets of clinical pharmacology of a drug that may impact drug disposition or action. These facets are pharmacokinetics, pharmacodynamics, specific dosing, and specific formulations.

-Pharmacokinetics

It is the concentrations of the drug that reach a specific organ or tissue and the time lasted in it. So pharmacokinetics determine the dose–concentration–effect relationship; namely, absorption, distribution, metabolism and excretion.

- *Drug Absorption*: the normal development of the child can affect the rate and extent of absorption, which depends on the gastric pH and the motility of the stomach and intestinal tract.

- *Drug Distribution*: the volume of distribution (VD) for a given drug may be affected by the sizes of body water and fat compartments. The amounts and distribution of body water and fat depend on a child's age and nutritional status.

Newborns have a higher sizes of body water (~75% TBW) than older infants and children. (RN, 2008). In the other hand, The body fat percentage in neonates is about 16% (57% water and 35% lipid).

The absolute concentrations of Albumin, total proteins, and total globulins are influenced by age, nutrition, and disease (Johnson TN, 2008)

- *Metabolism*: enzymes may be lacked or have markedly reduced activity in neonates so it is difficult to know how the drug will react when we give it to the newborns or infants. (Johnson TN, 2008) (RN, 2008)

- *Elimination*: GFR increases over the 1st few months. Modified renal drug clearance in the newborn and infants required different dosing recommendations. (Morselli PL, 1983)

Age-related pharmacokinetic changes affect the disposition of the drug and may cause an ineffective or toxicity response in children. (AA, 2011)

-Pharmacodynamics

Describes the relationship between the dose of the drug or its concentration and the response which may be desirable response *(effectiveness)* or unfavorable response (*toxicity).*

Age-dependent changes and Development can alter the action and the response to a drug. Little information available about the effect of human age changes on interactions between drugs and receptors and the impact of these interactions (Kearns G. L.-R., 2003).

-Age-specific dosing regimens

The age-associated changes in the absorption, distribution, metabolism, and excretion of drugs may determine the age-specific dose requirements (Kearns G. L.-R., 2003).

The lack of complete developmental profiles of the enzymes and the drug transporters prevent from using simple dosage formulas and algometric scaling. This techniques have reduced benefits in young infants and children, because of the age-related differences in drug disposition. However, these techniques may have a potential benefits in children older

than eight years of age and adolescents, because their organ function is similar to the adults (Alcorn, 2002). For example; Gentamicin is given to neonates in a dose of 2.5 mg/kg every 12 hours, to infants 2.5 mg/kg every 6–8 hours, to children 2.5 mg/kg every 8 hours and to adults 1–2 mg/kg every 8 hours because of apparent renal clearance and apparent volume of distribution. (Kearns G. L.-R., 2003).

-Pediatric drug formulations:

Acceptance of Formulations facilitate the adherence for medications in pediatrics, and may help in achieving the optimum outcomes. The acceptance of formulations is depends on the age groups. The dependence on caregivers at certain ages, also should be considered. To assure adequate medication adherence, we should minimize the discomfort, pain, and burden on the children and their caregivers (Bazzano, 2009).

The good taste is necessary to enhance the adherence of pediatric to oral formulations because pediatrics cannot tolerate for disagreeable tastes (Bazzano, 2009) (Kearns G. L.-R., 2003).

2.1.3 Infectious Diseases in Children:

Infections are the major diseases in children and infants and they are the massive reason for illness in day care and schools. Viral upper respiratory infections are the most common infection with children, and they have it multiple times in a year. Bacterial pneumonia and otitis media are also common diseases which can cause the child to end up having several antibiotic treatments. Diarrhea, skin infections, and poxes occur in children in winter, In addition to respiratory infections. (Noterman, 2016)

Infectious diseases are caused by pathogens (micro-organisms) that enter the body and causes different type of diseases, according to the pathogen. Theses pathogens might be bacteria, fungi or viruses. (Lumio, 2013). The human body's normal way of fighting invading micro-organisms is called inflammatory response, which occurs by increasing the number of white blood cells in the bloodstream. (Jalanko, 2014).

Common pediatric infections are Influenza, Common cold, Sinusitis, Otitis media Pneumonia, and Bronchitis.

-*Respiratory infections*:

Airways infections may be divided by upper and lower respiratory tract infections. The infection is named according to the area where the infection occurs, e.g. tonsillitis, pharyngitis, bronchitis …. (Hockenberry, 2013).

-Pneumonia:

The infection of the lungs may be caused by fungi, viruses or bacteria. Inflammatory waste and fluids accumulate into the lungs, cover alveoli and affect gas exchange in the lungs

producing problems in breathing. Pneumonia usually occurs secondary of previous upper respiratory infection, such as influenza. (Hockenberry, 2013)

RS-virus or influenza viruses are the main reasons of viral pneumonia. (Kalliola, 2015)

Bacterial pneumonia is mainly caused by pneumococcus or staphylococcus and it may be occurs as a secondary infection. (Hockenberry, 2013)

It is difficult to differentiate between bacterial pneumonia and viral pneumonia (Rajantie, 2010). Bacterial pneumonia usually occurs in the lower parts of the lungs and viral pneumonia in the upper part of the lungs and near the bronchus (Siimes, 2015).

Usually Blood tests are ineffective to distinguish bacterial from viral pneumonia. Some tests like C-reactive protein may be used. However, in some cases even though bacteria are affecting the lungs, CRP might be low. (Siimes, 2015)

Pneumococcus vaccinations prevent the resistant pneumococcus to penicillin caused pneumonias and are important to prevent pneumonia (Korppi, 2015).

-Bronchitis:

The Inflammation causes the bronchi to swell and partially obstructed because of the mucous (Jalanko, 2014).

Children who suffer from obstructive diseases such as asthma are more likely to have bronchitis because of the possibility of anaerobic bacteria (pneumococcus), to affect the surface of the bronchi (Kompare, 2012).

Healthy children may suffer from acute bronchitis caused by RS-virus or rhinovirus (Skjerven, 2015).

The symptoms of bronchitis are similar with the common cold; such as coughing and fever. Noisy breathing, elevated temperature, wheezing, and dry cough are the most characteristic symptoms of bronchitis. (Kompare, 2012).

-*Gastrointestinal (GI) infections:*

Gastrointestinal (GI) infections are one of the well- known causes of morbidity and mortality around the world. Mostly occurs due to viruses, and some are caused by bacteria and other organisms. In developing countries, the massive cause of mortality in infants and children is acute gastroenteritis**.**

Most mild diarrheas are not necessarily treated with Antibiotics, and empirical therapy for acute GI infections can be unnecessary antibiotic courses.

Bacterial GI most commonly caused by salmonella and shigella, whereas rotavirus, a double-stranded, wheel-shaped RNA virus is the most common cause of viral GI in infants and children. (Wells, 2015)

-*Urinary Tract Infection:*

Lower urinary tract infections include cystitis (bladder), urethritis, prostatitis, and epididymitis. Upper tract infections include the kidney and are referred to as *pyelonephritis*.

The major cause of uncomplicated UTIs is *E. coli,* accounting for more than 80% to 90% of community-acquired infections. (Wells, 2015).

2.2 Rational use of medications:

According to the World Health Organization, rational use of drugs means that the patient receives medications appropriate to his clinical needs, in the appropriate doses, for an adequate duration, and at the lowest cost (who, 1987).

2.2.1 Interventions to improve rationality in drug use:

There are three types of intervention strategies to improve rationality with drugs: educational, financial, and regulatory (Quick, 1991)

A. Interventions targeted at the prescribers levels:

1. Educational materials

Guidelines, flow charts, simple forms, and newsletters are the most educational materials used for prescribers (Le Grand A. H.-R., 1999). The common methods to deliver the educational materials for prescribers are: face-to-face communication, workshops, training, feedbacks and focus group discussions (Le Grand A. H.-R., 1999)

2. Regulatory strategies

Regulatory strategies like keeping unsafe drugs, and limiting its purchase from the market. However, it may not always be successful because that proses may result in black marketing of prevented drugs, and increase the irrational use of drugs.

B. Interventions targeted at patients level:

1. Educational interventions

A combination of two or more educational strategies and materials may be more effective with patients. Patient education is deference from public education. Face to face communication and writing consultation may improve patient compliance to the treatment.

General public education include booklets, posters, videos, mass media, role plays, and comics.

2. Regulatory strategies

The success of regulatory strategies may depend on the extent to which consumer behavior and request is addressed (Le Grand A. H.-R., 1999).

2.2.2 The process of rational treatment:

1- Identify the problem of the patient (diagnosis).
2- Specify therapeutic objectives (the goal of treatment).
3- Identify the suitability of the treatment (identify effectiveness and safety in this case).
4- Start the treatment.
5- Give instructions, informations, and warnings (use words the patient can understand).
6- Monitor (stop) the treatment (De Vries, 1994).

2.3 Irrational use of medications:

When one or more condition from the above is not met it means that the patient revived inappropriate treatment. (who, 1987). Also, irrational use of drugs can be because of the patient non adherence. Irrational use of drugs may include irrational drug selection, irrational dose selection, and irrational duration of therapy, drug interactions and lack of monitoring. (WHO, 2003)

2.3.1 Main problems of drug use:

1- Overuse of drugs and injections: overprescribing and overconsumption.
2- Polypharmacy: drugs prescribed are more than needed.
3- Wrong drug use: the inappropriate selection of a drug for a specific case, drugs of uncertain safety status, wrong dosage and incorrect duration. Incorrect drug use can be a mistake of the prescriber or a mistake of consumers. (Le Grand A. H.-R., 1999).

2.3.2 Effects of irrational use of medications:

1- Medical care effects: elevated mortality rates because of low quality and non-effective medications.
2- Antimicrobial effects: antimicrobial resistance.
3- Economic effects: increase the cost and budget on the patient and the companies.

2.4 Rational use of antibiotics:

Antimicrobial resistance (AMR) is the most difficult challenge in the 21st century (Cosgrove S. E., 2006). There are four factors may affect the future of AMR have been analyzed: microbial ecology; prescribing and dispensing of antibiotics; Fighting resistant bacteria; and health care policy. (DiLuigi, 2004) (Kocak, 2005) (Kaplan, 2013).

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

2.4.1 Rational Prescription of Antibiotics:

To choose the appropriate antibiotics we have to check the following points:

1- <u>The necessity of the antibiotic:</u>

Viruses are the common cause of infections and antibiotics may not treat viral infections or prevent secondary bacterial infections. In simple bacterial infections it is not necessary to give antibiotics because most of the simple infections overcome by themselves.

Locally in minor superficial infection Antiseptic may be used, but in the presence of abscess, the pus must be removed surgically. Then, if it is drained there is no need antibiotics (Niederman, 2005) (Lim, 1993).

<u>2- The selection of the antibiotic:</u>

Good antimicrobial effects can be obtained by rational and proper selection of antibiotics (Niederman, 2005). There are three factors should be taken into account when antibiotics are selected. These three major factors are:

a- *detecting of the pathogen*: The characteristics of pathogenic microbes helps in determine the route and duration of antibiotic therapy, and whether the pathogen is intracellular or extracellular are very important to take into account when choosing an antibiotics. Then antimicrobial susceptibility testing (AST) must be done to measure the ability of a particular organism growing in the presence of a specific antibiotic. 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 (Society, 1993).

b- *The antibiotics*: spectrum of the antibiotic, bioavailability, dosing schedule, patient tolerance, and antibiotics effects (bactericidal or bacteriostatic) all these properties contribute into the selection of the antibiotic.

c- *The patient*: There are many factors must be taken in account related to the patient and rational antibiotic selection.

These are as follows:

1. The severity of illness: dose must be adjusted to avoid accumulation and toxicity in patients with reduced renal or hepatic function or 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. Pregnancy and Lactation: specific considerations should be taken into account when using antimicrobial agents in pregnant women, which is related to both the pregnant woman and her baby.

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

5. History of Recent Antimicrobial Use: If the patient has been recently exposure to antibiotics (approximately 3 months), this can help to know that the microorganism that causes the current infection may have a resistant to that drug, and an alternative agent should be used.

The cost of an antibiotics is based on a lot of factors that like administration costs, prolonged hospitalization, adverse effects consequence, serum concentration monitoring and clinical efficacy (Niederman, 2005).

3- The indication of the treatment:

There are three indications for the antibiotics therapy:

- *Definitive Therapy*: It is for accurate diagnosis of bacterial infection. Testing microorganisms allows to recognize narrow spectrum, least toxic and cheap antibiotics (Nathwani, 1996).

- *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. 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 (Karim, 2004).

- *Prophylactic Therapy:* when the patient has risk of infection a prophylactic antibiotics should be taken and it is divided to:

  - Non-surgical prophylaxis: For example, traumatic injuries with a high probability of infectious complications and antimicrobial prophylaxis before dental or any other invasive procedures in patients having high susceptibility to bacterial endocarditis (Cusini, 2010).
  - Surgical prophylaxis: This is given mostly as a single dose before the surgery and is used to decrease 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, 2005).

4- The 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 and can be used for many indications. It is more convenient, cheaper, and reduced catheter infection risk while intramuscular route is less convenient for the patients and intravenous is used for severe disease of specific location (Kim, 2005).

5- The effectiveness of the treatment:

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 (Leekha, 2011).

2.5 Irrational Use of Antibiotics:

Incorrect and Inappropriate use of antibiotics occurs in both developing and developed countries. Sometimes Physicians prescribe antibiotics without indication and on the other side, sometimes patients do not follow their treatment instructions. This can lead to increase the antimicrobial resistance. Two thirds of all antibiotics are sold through unregulated private sectors and without prescription (Holloway K. &., 2011).

Low adherence levels by patients are a big problem. Many patients taking antibiotics for shortened duration or in under-dose. 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 (Holloway K. &., 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

2.5.1 Aspects of Inappropriate Use of Antibiotics:

1- Unnoticed indication for antibiotics.

2- Wrong selection of antibiotics.

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

4- Inappropriate combination

5- Unnecessary use of the costly antibiotics.

2.5.2 Causes of Irrational Antibiotics Use:

It is important to know the reasons why providers and consumers behave the way they do, in order to promote rational use of antibiotics (Holloway K. A., 2011).
The following reasons explain why people use antibiotics irrationally:

1-Health care level:

- The habit and knowledge of prescriber, it may take time to look up guidelines for prescribing

- 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 (Haaijer-Ruskamp, 1996)

2-National level:

- Poor availability of government-funding for education and supervision of medical staff which includes prescribing process. (Le Grand A. H.-R., 1999)

3-Community level:

- Patient-dispenser interaction time is very short (may be seconds) that does not allow sufficient time to explain to patients how to take their medicines.

- Self-medication and self-administration of antibiotics without prescription and sometimes without indication (Le Grand A. H.-R., 1999).

2.5.3 The Consequences of Irrational Use of Antibiotics:

1- **Adverse, possibly lethal effects:** when doses are not adjusted properly it may accumulate to a toxic level and have direct toxicity on patients (WHO, 1977).

2- **Limited efficacy:** when under-therapeutic dosage of antibiotics is given to the patients.

3- **Super infection:** When antibiotics are administered it will kill the normal flora which live and have benefit from living in the body but do not cause harm to the

body. Then pathogenic drug-resistant organisms can flourish because of the absence of competition. This is considered as super infection (Coenen, 2007).

4- **Bacterial Resistance**: resistance is defined as "the acquired ability of bacteria to survive in the presence of concentrations of a chemical which are normally lethal (Cantón, 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 (WHO, WHO fact sheet no. 194, revised January 2002, 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, 2005).

5- **Economic effects:** excessive cost and prolonged disease and hospitalization cause both patient and health care system to spend excessively on pharmaceuticals and this will be leading to waste of financial resources because of Over-use or incorrect use of antibiotics (Nash, 2002). Also Antimicrobial resistance costs annually $4000-5000 million in the USA and 9000 million in Europe (Holloway K. &., 2011).

2.6 Principles of antimicrobial therapy in pediatric:

Reducing unnecessary antibiotic use are important targets for Pediatric populations. Environments unique to children, such as schools and day care, increase the spread of antibiotic resistance (Cherian, 1994) (Henderson, 1988). The duration and frequency of prior antibiotic exposure are associated with the spread of antibiotic resistance and children receive a significant proportion of the total antibiotics prescribed each year (Nyquist, 1998).

To reduce the usage of unnecessary antibiotic in pediatrics, we have to identify the conditions for which antibiotics are overprescribed (McCaig L. F., 1995).

Important considerations in using antimicrobials with pediatrics:

1- Cultures must be obtained in potentially serious infections. Empiric antimicrobial therapy may be started, then should be modified based on the culture results and to the patients' response. Sometimes several same safe and effective antimicrobials are available. So in this situation, the ease of administration and cost of the different choices should be considered.

2- Other important considerations include the patient's medical history, age, and immune status. In Neonates and young infants it is difficult to distinguish serious disease from mild illness because they may present with nonspecific signs of infection. In older children, clinical diagnosis is more specific, which may permit therapy to be avoided or allow use of a narrower-spectrum antibiotic.

3- Immune suppressive patients may be susceptible to more types of potential infecting pathogenic that need to be considered, including organisms that are usually virulent but may cause infections that are serious and difficult to treat.

4- Another important consideration is the seriousness of the illness. A severe and rapidly progressive illness must be treated initially with a broad-spectrum antimicrobial until a specific etiologic diagnosis is made. A mild ill outpatient should receive treatment preferentially with narrow- spectrum antimicrobials.

5- Some antimicrobials have not been approved (and sometimes not tested) for use in newborns. For those that have been approved, it is important to recognize that both dose and frequency of administration may need to be altered especially in young (7 days or younger) or low-birth-weight neonates (≤ 2000 g).

6- Antimicrobial agents excreted and metabolized through various physiologic mechanisms (e.g., renal, hepatic), so It is important to follow up these routes of excretion and alter the antimicrobial doses according to the organ function.

7- Serum levels of drugs with a high risk of toxicity (e.g., aminoglycosides) are ordinarily measured. Also, the measurement of other drugs (e.g., vancomycin) may be useful in selected circumstances (Doherty, 2006)

2.7 Strategies and plans to improve guideline implementation and rational administration of antibiotics in pediatric:

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 (WHO, 2013).

Important strategies needed to stop or decrease antimicrobial resistance and provide rational antibiotic therapy are:

(1) Improve living conditions to reduce the spread of infections, e.g., nutrition, education, and immunization.

(2) National organization for antibiotic marketing.

(3) The availability of effective agents at a suitable cost to the greatest need population.

(4) A network of distribution to ensure that effective agents are delivered to the population rationally.

(5) A medical care system that can diagnose and manage the infectious diseases in a good level of accuracy in the absence of sophisticated technology (Kunin, 1987).

(6) Laboratory systems and community control to detect resistant microorganisms and help health care providers in the selection of effective antibiotic at a suitable cost.

(7) Understanding of beliefs, habits, and tradition related to the health and diseases in a specific served population.

(8) Education system for the health care providers about the medical care needs of the population includes management-oriented disease classification based on critical clinical signs (Kunin, 1987).

2.7.1 The Centers for Disease Control and Prevention's 12 Steps to Prevent Antimicrobial Resistance in Hospitalized Adult:

Prevent infection
1. Vaccinate
2. Get the catheters out

Diagnose and treat infection effectively
3. Target the pathogen
4. Access the experts

Use antimicrobials wisely
5. Practice antimicrobial control
6. Use local data
7. Treat infection, not contamination
8. Treat infection, not colonization
9. Know when to say "no" to vancomycin
10. Stop treatment when infection is cured or unlikely

Prevent transmission

11. Isolate the pathogen
12. Break the chain of contagion (Cosgrove S. E., 2007)

2.7.2 Antibiotic Stewardship Program:

Antibiotic stewardship defined by the Infectious Diseases Society of America (IDSA), the Pediatric Infectious Diseases Society (PIDS), and the Society for Healthcare Epidemiology of America (SHEA) as "coordinated interventions designed to improve and measure the appropriate use of [antibiotic] agents by promoting the selection of the optimal [antibiotic] drug regimen including dosing, duration of therapy, and route of administration" (Fishman, 2012)

Recommendations for Implementation of Antibiotic Stewardship Program:

1. Preauthorization and/or prospective audit and feedback over no such interventions.

Preauthorization is a process that improve the usage of antibiotics by getting approval from clinicians for certain antibiotics before they are prescribed. Prospective audit and feedback (PAF) means that the provider will be engaged after an antibiotic is prescribed.

Preauthorization decreases the use of unnecessary or inappropriate antibiotics, Optimizes empiric choices and influences downstream use, encourages the review of clinical information and cultures at the time of the treatment, reduces the cost of antibiotics and Direct control over antibiotic use. But in the other hand, It may affects only the use of restricted agents, Addresses empiric use to a much greater degree than downstream use, No prescriber autonomy, It can retard the therapy, Effectiveness based on the approver skills, Time consuming, Potential for cheating (e.g., gain approval in a biased manner) and May simply shift to other antibiotic agents and select for different antibiotic-resistance patterns.

Prospective Audit and Feedback Increase the reality of antimicrobial stewardship program and make collegial relationships, enhancing uptake by prescribers thus, more clinical data will be available for recommendations, increase flexibility in the time of recommendations, If resources are limited it can be done on less than daily basis, Provides educational benefit to clinicians, Prescriber autonomy maintained, and it Can address de-escalation of antibiotics and duration of therapy. But this way my have some disadvantages such as: Success may be based on the way that produce the feedback to prescribers, Prescribers may not be agree to change therapy if patient is doing well, Identification of interventions may require information technology support and/or purchase of computerized surveillance systems and it May takes longer to achieve reductions in targeted antibiotic use (Barlam, 2016)

2- Educational materials for stewardship:

To complete stewardship effectiveness, Passive educational activities should be used. For example, lectures, informational pamphlets, Academic medical centers and teaching hospitals. These educational activities should integrate on fundamental antibiotic stewardship principles in hospitals into their preclinical and clinical curricula (Barlam, 2016).

3. Development of facility-specific clinical practice guidelines coupled with a dissemination and implementation strategy:

Practice guidelines and algorithms are effective ways to rationalize prescribing of antibiotics. ASPs must develop those guidelines for common infectious diseases.

4. Implementing interventions to improve antibiotic use and clinical outcomes that target patients with specific infectious diseases syndromes.

5. The use of strategies (e.g., antibiotic time-outs, stop orders) to encourage prescribers to perform routine review of antibiotic regimens to improve antibiotic prescribing:

Antibiotic "Time outs "technique means that continuing review of the need and selection of antibiotics when more diagnostic information is available. The antibiotic therapy have to be reviewed by clinicians 48 hours after antibiotics are initiated (Levy M. M., 2014)

7. Incorporation of computerized clinical decision support at the time of prescribing into ASPs.

8. Implement programs to increase both the timely transition of patients from IV to oral antibiotics and appropriate use of oral antibiotics for initial therapy.

9. Implementation of guidelines and strategies to reduce antibiotic therapy to the shortest effective duration.

10. The use of rapid viral testing for respiratory pathogens to reduce the use of inappropriate antibiotics.

11. Measurement of antibiotic costs based on prescriptions or administrations instead of purchasing data. (Barlam, 2016).

2.8 Previous studies regarding rational antibiotics use:

A descriptive, cross-sectional survey conducted to determine the current prescribing practices at Hawassa University Teaching and Referral Hospital. The study shows The most commonly prescribed antibiotics were amoxicillin (16.4%), ampicillin (15%), gentamicin (14.9%) and chloramphenicol (11.6%). On the other hand, the most commonly prescribed injections were ampicillin (21.4%), cloxacillin (13.4%), crystalline penicillin (12.4%), ceftriaxone (9.8%) gentamicin (9.8%), diclofenac (9.4%), chloramphenicol 41 (8.4%) and furosemide 25 (5.1%) (Desalegn, 2013).

In a study conducted in Turkey (Ertugrul, 2009), 38 (54.3%) of the hospitalized patients was receiving antibiotics. At the end of study, it was found that only 12 (32%) of the patients who were on antibiotic use were receiving the agents rationally. 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.

Also, there is a study that was carried out in Turkey and 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 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 (Gül, 2013).

A Retrospective study conducted by reviewing of medical records was performed for all children (aged 1 month to 16 years) admitted in a closed multidisciplinary-cardiothoracic PICU from January to June 2013 in India. The study shows that the Most commonly used antibiotics were cefazolin, meropenem, vancomycin and ceftriaxone, and most frequently used combination was meropenem and vancomycin. In most cases, (70%) empiric antibiotic combinations were stopped in 72 h (Abbas, 2016)

A cross-sectional study was conducted in Buali Sina hospital by using the records of patients hospitalized between 22 Sep 2010 and 21 Sep 2011. Data of different wards including Neonatal, NICU, PICU, Pediatrics and Pediatric surgery were separately extracted and analyzed. Drug consumption data were expressed as DID (daily defined dose per 100 Inhabitant per day). A total of 4619 in-patients records during 1 year of study

including 2494 patients in fall and winter and 2125 patients in spring and summer were evaluated. The most hospitalized patients were in Pediatric ward (43.9 %). The highest DID value were obtained for ceftriaxone (21.7), ampicillin (6.05) and vancomycin (4.7), while the lowest value was for gentamicin (0.01). In both cold and warm seasons, Ceftriaxone was the most frequent prescribed antibiotic (Salehifar, 2014).

A study in which Data at the pediatric departments of two hospitals was collected, for 3 years (2008–2011). Broad-spectrum antibiotics were the most commonly prescribed antibiotic class in both hospitals, especially third generation cephalosporin, (69%) (Sharma, 2015).

3-METHODOLOGY:

3.1 Study design:

A retrospective study of antibiotic utilization patterns in pediatrics between 1st September 2017 and 30th September 2018. Patients' information and data was obtained from patient archives and electronic records in Near East university hospital (NEUH).

3.2 Setting:

This study was carried out in Near East university hospital (NEUH) in Northern Cyprus. The hospital is one of the largest leading medical facilities in Cyprus. The 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.

3.3 Study subjects

All pediatric patients' archives was reviewed and extracted by two trained research pharmacists during October and November, 2018. Patients matching the following criteria were included in the analysis.

Inclusion criteria:

- All patients younger than 18 years of age,
- Admitted to NEU hospital within the study time frame (1st September 2017 till the 30th of September 2018).
- Patients who used at least one antibiotic during hospitalization.

Exclusion criteria:

- Patients with incomplete files or missing information.
- Patient who stayed less than one day in the hospital.

3.4 Data Extraction:

Patient demographic details, e.g., gender, age, weight, prescribed antimicrobials, number of doses per day, frequency and route of administration were obtained from the hospital archive. Lab tests, medical history, cultures and radiograms were obtained from the hospital electronic database.

3.5 Guidelines and clinical resources:

The rationality of Antibiotic prescriptions were analyzed using Infectious Diseases Society of America (IDSA), Centers for Disease Control and Prevention (CDC) guidelines , Up TO Date, world health organization (WHO) e-pocketbook guidelines,.

The rationality of antibiotic prescriptions analyzed by an infection physician, pharmacologist, clinical pharmacist and a researcher step by step looking to the drug selection, dose, rout of administration, duration of therapy, lab tests and cultures each case individually.

3.6 Statistical analysis:

The collected and analyzed data were conducted using Microsoft Excel 2016 and statistical package for the Social Sciences (SPSS), software version 18.0. We used descriptive statistic to analyzed continuous data and used crosstab and correlation test for categorical data. Chi-square test, fisher extract test and t test were used in the statistical analysis.

3.7 Ethical Consideration

Privacy of the patient was assured during the study. The study was approved by the Near East Institutional Review Board (IRB) of Near East University Hospital that assigned this research as being just an observational study. Private patient data were not recorded. The medical record and patient's profile approved to be obtained from the NEU pediatric department archives

4-RESULTS:

4.1 Study Sample and patient characteristics:

There were 332 pediatric patients admitted to NEUH during 1st September 2017 and 30th September 2018. 229 patients were using antibiotics and were included in the analysis. Of them 107 (46.7%) were females and the rest 122 (53.3%) were males. The age classification of patients were as follows: neonates 140(61.1 %), infants 30(13.1%), children 57(24.9 %), and adolcent 1(0.4%).

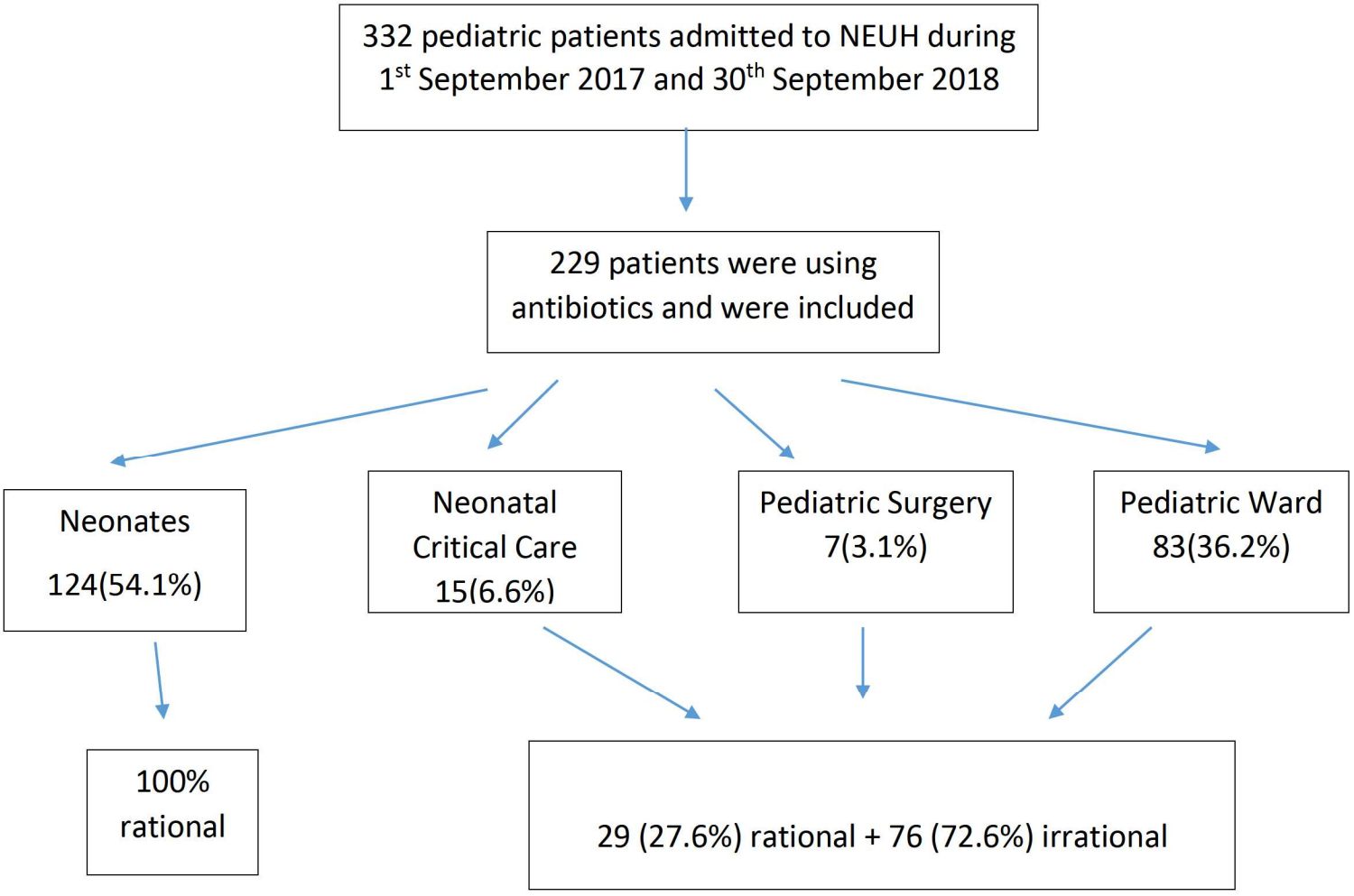

Figure 1: Study Sample and patient characteristics.

Table 1: CHARACTERISTCS OF PATIENTS:

CHARACTERISTCS OF PATIENTS		
GRNDER	N	%
Female	107	46.7%
Male	122	53.3%
AGE		
Nconatcs	140	61.1%
Infants	30	13.1%
Children	57	24.9%
Adolcent	1	0.4%
Clinics		
Neonatal Critical Care	15	6.6%
Neonates (newborns)	124	54.1%
Pediatric Ward	83	36.2%
Pediatric Surgery	7	3.1%
Rationality		
Rational	153	66.8%
Irrational	76	33.2%

Patients that stayed in the hospital about one or two days was 113(49.1%) and the rest of patients 116(50.9%) stayed more than 2 days.

In the pediatric clinic, the highest number of patients admission to the hospital was in January 16 (19.3 %) followed by September 8(9.6 %), and most of patients stayed about 2 days in the hospital 24 (28.9%) while they received antibiotic therapy on average for 2 days too.

4.2 Antibiotics indications and utilization:

All newborns 124 (54.1%) were given neomycin 108(87.1 %) or polymyxcin 16(12.9 %) topically.

Regarding other patients 104 (45.9%), the most common reason for antibiotic usage were lower respiratory infections 42 (40.4%), then preterm newborns 15 (14.4%), gastrointestinal infections(GI) 13 (12.5%), upper respiratory infections 11 (10.6%), urinary tract infection(UTI) 7 (6.7%), surgery 7 (6.7%), meningitis 2 (1.9%), appenditis 2 (1.9%), candida 2 (1.9%), asthma 1 (1%), coma 1 (1%) and viral sundrom1(1%).

Most of these patients received one antibiotic 61 (58%), while 40 (38.5%) patients received two antibiotics and only 3(2.9%) patients received up to 3 antibiotics at the same time.

Table2: diagnosis of patients

	N	Percent
Pneumonia	42	40.4%
Pre Term Newborns	15	14.4%
GI infection	13	12.5%
Pharyngitis	11	10.6%
UTI	7	6.7%
Surgery	7	6.7%
Meningitis	2	1.9%
Appenditis	2	1.9%
Candida	2	1.9%
Asthma	1	1.0%
Viral Syndrome	1	1.0%
Coma	1	1.0%
Total	104	100.%

The most commonly used antibiotics for newborns was neomycin 108(87.1 %) , while for other patients ceftriaxone was the most prescribed antibiotic 59(28.4%), followed by clarithromycin 28(13.5%), ampicillin-sulbactam 26(12.5%), and gentamycin 18(8.7%). In terms of groups also cephalosporin 64 (20.6%) were the most commonly used antibiotic group, followed by penicillins 30 (9.6%), macrolides 29 (9.3%), and aminoglycosides 18 (5.8%). Other antibiotics groups that were used include antiprotozoals 4 (1.3%), antifungals 3 (1%), antivirals 2 (0.6%) and carbapenems 1 (0.3%)

Table 3: Antibiotics used:

	N	Percent
Ceftriaxone	59	28.4%
Clarithromycin	28	13.5%
Ampicillin-Sulbactam	26	12.5%
Gentamycin	18	8.7%
Amoxicillin-Clavunate	4	1.9%
Nistatin	3	1.4%
Metronidazole	4	1.9%
Cefazolin	5	2.4%
Ostelmavir	1	0.5%
Meropenem	1	0.5%
Acyclovir	1	0.5%
Azithromycin	1	0.5%
		.

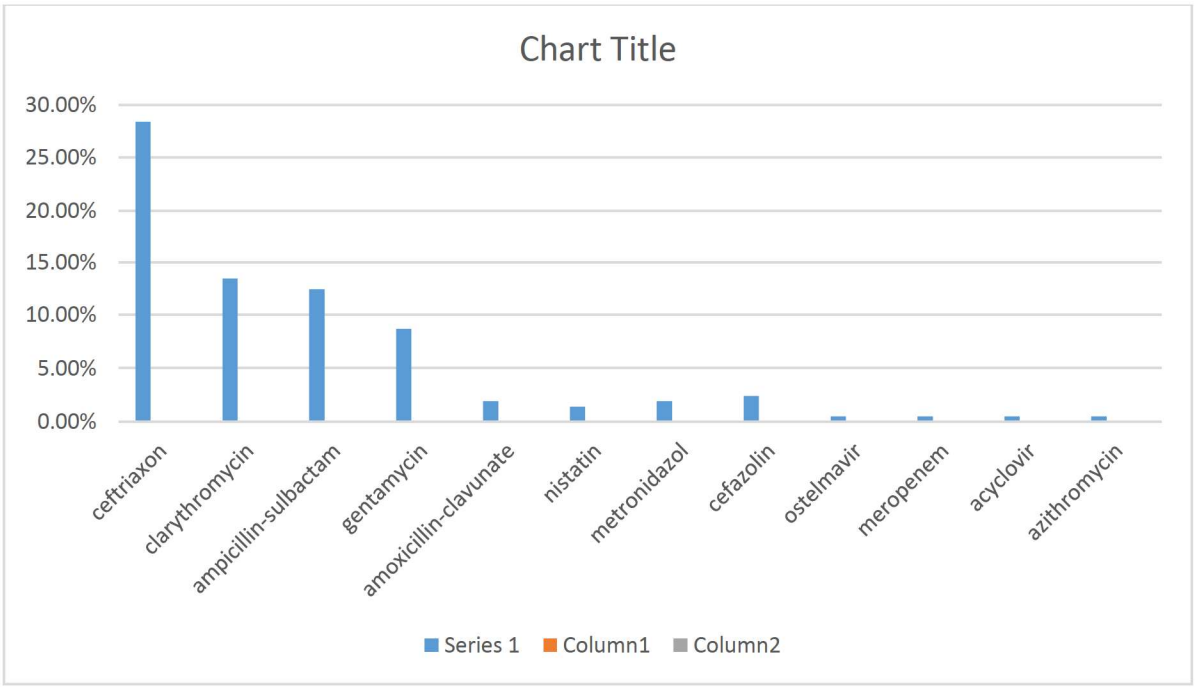

Figure 2: Antibiotics used.

The most common route of administration used in the hospital was IV 115(37%), po 30 (9.6%), IM 4 (1.3%) and topical 2 (0.6%).

Table 4: Rout of administration:

Rout of administration	N	Percent
IV	115	37.0%
IM	4	1.3%
PO	30	9.6%
TOPICAL	2	0.6%

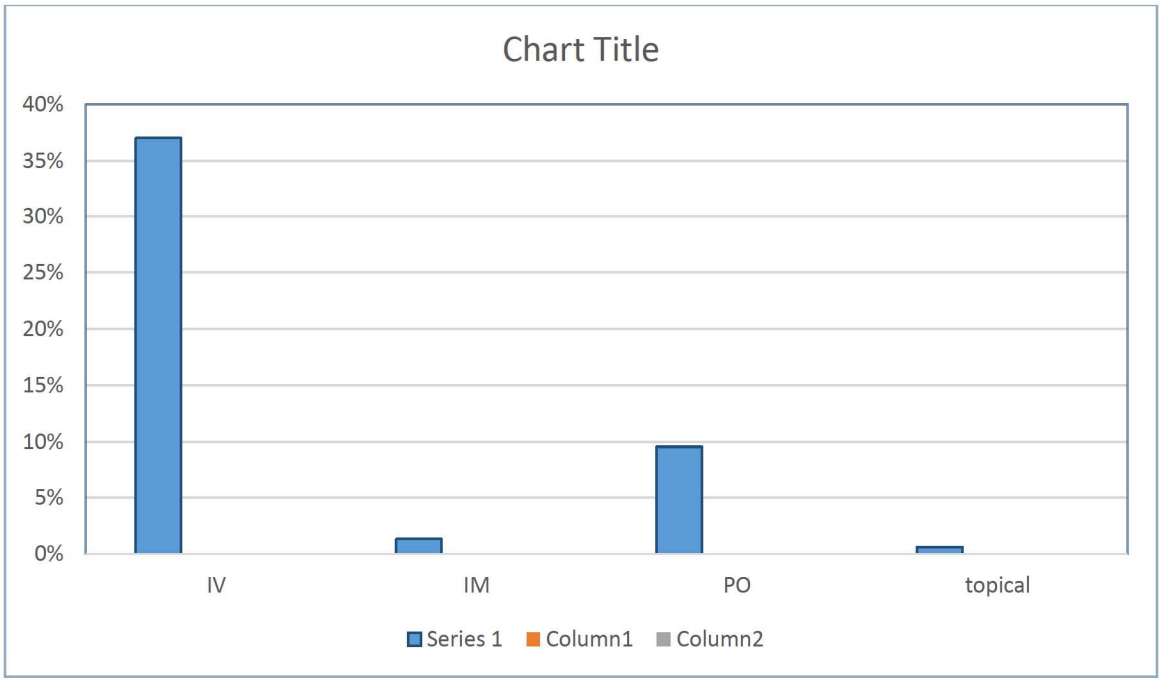

Figure3: Rout of administration.

4.3 Rationality of prescribed antibiotics

In general 153 (66.8%) of the patients including newborns received antibiotics rationally while 76(33.2%) were identified as irrational. All newborns 124 (54.1%) were identified as rational 100(100%) as topical neomycin or polymexcin were used in compliance with guidelines.

NICU patients had the highest irrationality15 (100%), followed by pediatric ward patients 58 (69.9%). In terms of age groups, preterm age was significantly associated with irrational antibiotic use practice. No significant differences were found in the distribution of rationality between male and female patients. Also there is significant association between rationality and duration of stay ($p<0.001$).

Table 5: Rationality among clinics:

CLINICS	RATIONAL		IRRATIONAL	
	N	PERCENT	N	PERCENT
NICU	0	0%	15	100%
Pediatric Surgery	4	57.1%	3	42.9%
Neonates	124	100%	0	0%
Pediatric	25	30.1%	58	69.9%

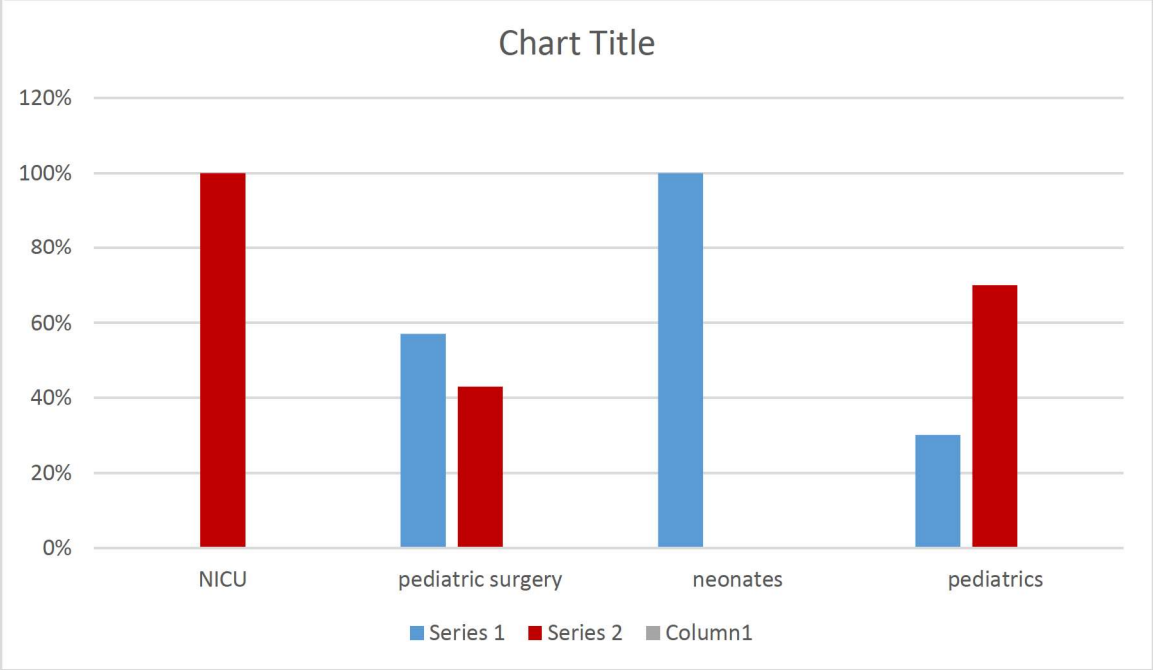

Figure 6: Rationality among clinics

Preterm newborns infections was the most commonly associated disease with an irrational antibiotic use practice ($p<0.001$) followed by Pneumonia ($p<0.001$). The most common identified problem was prolonged empirical therapy 39(12.5%), followed by Irrational drug selection 30(9.6%) ($p<0.001$)(Table 4).

Table 6: Types of drug problems detected with the patients:

Drug problems	N	Percent
Prolonged empirical therapy	39	17.03%
Irrational drug selection	30	13.1%
Drug monitoring required	13	5.7%
High dose	8	3.4%
Low dose	4	1.7%
Unnoticed indication	2	0.9%
More medication required	2	0.9%
Short duration	1	0.4%
Drug interaction	1	0.4%
Second line	1	0.4%
Inappropriate combination	1	0.4%

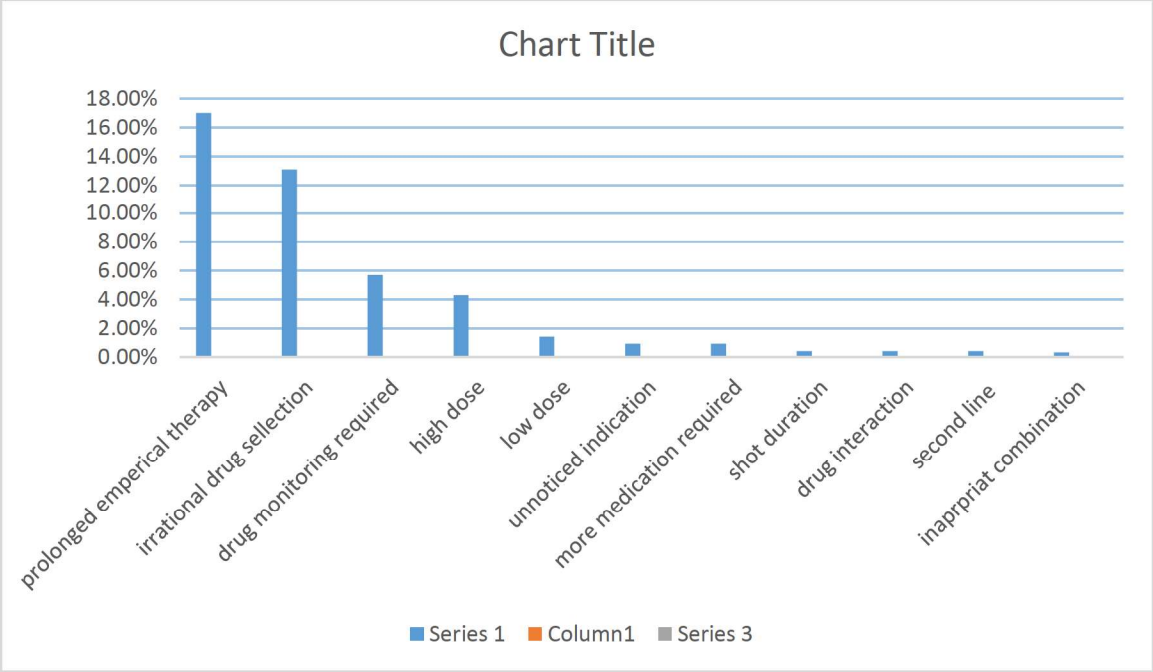

Figure 5: Types of drug problems detected with the patients.

Table 7: prolonged empirical therapy for patients stayed in the hospital more than 2 days without culture:

Culture	**Duration**			
	2 Or Less Than 2		More Than 2 Days	
	N	**%**	**N**	**%**
Did Culture	12	11.5%	30	28.8%
No Culture	18	17.3%	44	42.3%

5-Discussion:

General antibiotics use patterns had been associated with unsafe use, waste of resources, non-adherence, excess adverse drug reactions and disease resistance (Quick, 1991). Improvement of rational antibiotic use can be obtained by identifying the most common causes for irrational use of drugs. All countries must identify these causes and problems by conducting operational research for surveillance of antibiotic use using both qualitative and quantitative techniques (Quick, 1991). The cost of irrational drug use is very massive for patients and the community (Hogerzeil, 1989).

Increasing the resistance to antimicrobials has been recognized as a worldwide threat to the health of public (Tornimbene, 2018). About 60% of antibiotics still used irrationally in hospitals (Gerber J. S., 2013).

Limited information about antibiotic use with pediatrics in hospitals are available, even so antibiotics are the most medications administered to pediatrics (De Jong, 2009) (Schindler, 2003). According to The American Academy of Pediatrics guidelines, few studies have focused on hospitalized newborns, children, and adolescents (Dellit, 2007). Most of pediatric patients have been treated with antibiotics during their hospitalization and many of these prescriptions were inappropriate (Smith M. J., 2015) (Levy E. R., 2012).
This study was carried using retrospective observational study design to assess the use of antibiotics with pediatrics and identify the problems and challenges that prevent from rational administration of antibiotics and increase the antimicrobial resistance.

Only 27.9% of patients received antibiotics rationally without any problems, but 70.1% of patients had at least one drug related problem with their antibiotic treatment. Other studies reported (39%) irrationality in Colombia, (97%) in Pakistan, 68% in Turkey. The most common identified problem was missing culture (12.5%) especially with lower respiratory infections (64.3%) leading into prolonged empirical therapy. **Ertugrul, M. B** (Ertugrul, 2009)Et al identified as the most common problem in their study population 50% while **Gül, H. C** (Gül, 2013)et al identified as the most common problem 54.3%. In our study 42.3% of patients stayed in the hospital more than two days without doing culture for them and without changing the empirical therapy. 85.7% of UTI patients and 76.9% of GI patients were had inappropriate antibiotic selection.

In a study on prescribing patterns was conducted at the Children's Clinical University Hospital in Latvia (2018), they found that The most commonly used antibiotic group was other-lactam antibiotics 76% (Sviestina, 2018). Another study about medical records of in pediatric (age 1 month–16years) found that broad-spectrum antibiotics were the most prescribed antibiotics, especially third generation cephalosporin (69%). (70%) empiric antibiotic combinations were stopped in 72 h (Abbas, 2016). Also a cross-sectional study in Buali Sina hospital covered different clinics including Neonatal, NICU, PICU, Pediatrics, and Pediatric surgery found that the most hospitalized patients were in Pediatric

ward (43.9 %). And the most commonly used antibiotics were ceftriaxone (44.8%), amikacin (14.8%) and ampicillin (14.5%). In both cold and warm seasons, Ceftriaxone was the most frequent prescribed antibiotic (Salehifar, 2014).

Increased use of cephalosporin especially broad spectrum ones may cause the disaster of antimicrobial resistance and the overgrowth of pathogenic microorganisms (Gagliotti, 2006) (Mousavi, 2013). It is a global problem that may influence antimicrobial resistance all over the world. Broad spectrum antibiotics mustn't be used in simple cases where a narrow spectrum antibiotic can be used.

In our study we also found that Ceftriaxone is the most commonly used antibiotic (28.4%) especially in meningitis (100%), GI (76.9%), lower respiratory infections (73.8%) and UTI (71.4%). There were 2 patients had an allergy to cephalosporin were given ceftriaxone.

All Preterm neonates were administrated gentamycin and ampicillin-sulbactam to prevent the respiratory infections that may occur with the neonates if an aspiration of any microorganism happened during delivery. Although it is rational prophylaxis, drug interval, culture, plasma concentration and total dug monitoring are required to prevent the toxic effects of gentamycin. The duration must be at least 2 days and can be continued up to 7-10 days if there were any signs of infection (Dahl, 1986) (Fuchs, 2018).

86.7% of preterm neonates in our sample 15 (14.4%) were given gentamycin and ampicillin-sulbactam without the required monitoring, 100% without plasma concentration, 100% without dose interval, 93.3% without culture and no information about the health of their mothers.

In (2007) a study has reported concern about the continuous and excessive use of antimicrobial agents that cause the emergence of antibiotic-resistant organisms. Evaluating antibiotic prescription and monitoring of antimicrobial uses are strategies recommended for management of resistance to antimicrobials in hospitalized patients. Also several studies report Antimicrobial resistance raises already-rising health care costs and increases patient morbidity and mortality (Katakam, 2012) (Ochoa, 2000).

The implementation and improvement of (Antibiotic Stewardship program) ASPs in pediatrics is increasing. A survey of 38 hospitals within the Children's Hospital Association (CHA) found that 16 had a formal ASP, and an additional 15 were planning to implement a program (Newland, 2014). Antimicrobial stewardship programs are important to ensure that the patients receive targeted therapy. Most hospitals that did not implant a ASPs performed one or more stewardship activities; formulary restriction, prospective-audit-with-feedback, and used clinical guidelines (Smith M. J., 2015).

A study about the benefits of ASP found a 14% decrease in antibiotic-days of restricted antimicrobials and an 11% decrease in daily doses in the first year of a web-based ASP on antimicrobial use. Also, a 12% reduction in daily doses of unrestricted antimicrobials has been reported. At the same time, a decrease of $370,069 in the costs of limited antibiotics

has been reported after the first year of their ASP and increased the physician satisfaction with the ASP, from 22% to 68% after implementation (Agwu, 2008).

Pharmacists play a crucial role in the development and implementation of antimicrobial stewardship programs for both primary and secondary care, hospitals and the development of antimicrobial prescribing guidance (MacDougall, 2005) (McNulty, 2012) (Goff, 2017).

Pharmacists are very close to the patients so they can be a part of the clinical teams that work on producing the rational antimicrobials to the patients. Also, pharmacists can help in determine which agents and treatment plans that confirm with the national standards that apply in their countries (WHO, 2016)

The SHEA and IDSA guidelines state that the team of antimicrobial stewardship include an infectious diseases physician and a clinical pharmacist with infectious diseases training. Pharmacists are drug experts, so they play an important role in ASPs. Children have special therapeutic considerations, so they need a pharmacist who have enough knowledge of their unique medical issues. Also, pediatrics have especial pharmacokinetics, dosing requirements, antimicrobial formulation needs, and antimicrobial susceptibility profiles, and pharmacists are an excellent resource for knowledge of these topics (Gerber J. S., 2010).

A study in USA about Changes in Antimicrobial Agent Usage Resulting from Interactions Among Clinical Pharmacy, patient outcomes showed that improvement in the patients' condition was accomplished in >90% of cases in which an intervention was made. Real dollar expenditures for antimicrobial agents declined by >$200,000 per year (Schentag, 1993).

Strength and Limitations:

This study is the first to assess antibiotic use in pediatric in Northern Cyprus and in Turkey.

In the current study, not only the antibiotic usage patterns and utilization was identified and described, yet also antibiotics associated drug related problems were assessed and classified accordingly. The study involved 12 months duration and involved relatively a large sample of patients.

Patients were enrolled from all pediatric clinics including neonates, NICU, surgery and pediatrics.

In spite those strengths mentioned, the retrospective design of the study have many limitations, as much information is missing due to poor documentation and no patients progress note recorded, beside known limitations of such study designs. Also patient discharge plans were not recorded thus discharge antibiotics were not involved. All these beside the uni-center design of the study may limit the generalizability of the study findings.

5.1: Conclusion:

Children have unique medical needs related to antimicrobials and thus deserve focused efforts.

Drug monitoring and missing cultures are the most common reasons for irrational antibiotic use in our study leading to prolonged empirical therapy and adverse reactions. Also the selection of the antibiotic must be according to the guidelines and local synthesized data and protocols. The high usage of Ceftriaxone, was a prominent finding.

Strategies for more justified administration of antibiotics especially broad –spectrum ones are necessary.

We will be able to decrease irrational use of antibiotics by implementing the Antimicrobial stewardship programs.

Children have special considerations compared with adults when it comes to pharmacotherapy, so it is necessary that a pharmacist advocating on behalf of the pediatric patient have intimate knowledge of their unique medical issues.

More prospective studies are needed to assess the rational use of antibiotics with pediatrics. Also, assessing the knowledge of rational antibiotic use of the healthcare providers and their sources of rational information are needed.

References

AA, V. (2011). Important role of population pharmacokinetic/pharmacodynamics.

Abbas, Q. H. (2016). Evaluation of antibiotic use in Pediatric Intensive Care Unit of a developing country. *ndian journal of critical care medicine: peer-reviewed, official publication of Indian Society of Critical Care Medicine,*.

Abdel-Rahman SM, K. G. (2009). The pharmacokinetic-pharmacodynamic.

Agwu, A. L. (2008). World Wide Web–based antimicrobial stewardship program improves efficiency, communication, and user satisfaction and reduces cost in a tertiary care pediatric medical center.

Alcorn, J. &. (2002). Ontogeny of hepatic and renal systemic clearance pathways in infants part I.

Barlam, T. F. (2016). mplementing an antibiotic stewardship program: guidelines by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America. *Clinical Infectious Diseases*.

Bazzano, A. T.-S. (2009). Off-label prescribing to children in the United States outpatient setting.

Besançon, L. (2016). Antimicrobial resistance. What will it take to turn the tide? Pharmacists! *Journal of Pharmacy Practice and Research, 46(1), 4-5.*

Besançon, L. (2016). ntimicrobial resistance. What will it take to turn the tide? Pharmacists! *ournal of Pharmacy Practice and Research, 46(1), 4-5.*

Bielicki, J. L. (2015). Antimicrobial stewardship for neonates and children: a global approach. *The Pediatric infectious disease journal,*.

Cantón, R. C. (2003). Multi-resistant Gram-negative bacilli: from epidemics to endemics. *Current opinion in infectious diseases,*.

cdc. (2011). center for disease control and prevention.

Ceci, A. F. (2002). Medicines for children licensed by the European Agency for the Evaluation of Medicinal Products. *European journal of clinical pharmacology, 58(8), 495-500.*

Cherian, T. S. (1994). A cluster of invasive pneumococcal disease in young children in child care.

Coenen, S. F.-R. (2007). European Surveillance of Antimicrobial Consumption (ESAC): quality indicators for outpatient antibiotic use in Europe. *BMJ Quality & Safety,* .

Cosgrove, S. E. (2006). he relationship between antimicrobial resistance and patient outcomes: mortality, length of hospital stay, and health care costs. *Clinical Infectious Diseases*.

Cosgrove, S. E. (2007). Impact of different methods of feedback to clinicians after postprescription antimicrobial review based on the Centers For Disease Control and Prevention's 12 Steps to Prevent Antimicrobial Resistance Among Hospitalized Adults. *nfection Control & Hospital Epidemiology,*.

Cusini, A. R. (2010). Different patterns of inappropriate antimicrobial use in surgical and medical units at a tertiary care hospital in Switzerland: a prevalence survey. *PloS one, 5(11), e14011.*

Dahl, L. B. (1986). Serum levels of ampicillin and gentamycin in neonates of varying gestational age.

De Jong, J. V.-v. (2009). Antibiotic usage, dosage and course length in children between 0 and 4 years.

De Vries, T. P. (1994). Guide to good prescribing: a practical manual.

Dellit, T. H. (2007). Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America guidelines for developing an institutional program to enhance antimicrobial stewardship.

Desalegn, A. A. (2013). Assessment of drug use pattern using WHO prescribing indicators at Hawassa University teaching and referral hospital, south Ethiopia: a cross-sectional study. *BMC health services research,*.

DiLuigi, A. J. (2004). Prophylactic antibiotic administration prior to hysterectomy: a quality improvement initiative. *The Journal of reproductive medicine*.

Doherty, G. M. (2006). Current surgical diagnosis & treatment .

Ertugrul, M. B. (2009). Bir Üniversite Hastanesi Cerrahi Servislerinde Antibiyotik Kullanimi ve Maliyeti: Bir Günlük Nokta Prevalansi Çalismasi/Antibiotic Use and Its Cost in Surgical Clinics of a University Hospital: A One-Day Point Prevalence Survey. . *Klimik Dergisi*.

Esposito, S. B. (2001). Use of antimicrobial agents for community-acquired lower respiratory tract infections in hospitalised children. *European Journal of Clinical Microbiology and Infectious Diseases, 20(9), 647-650.*

FDA. (2003). Guidance for Industry.

Fishman, N. S. (2012). Policy statement on antimicrobial stewardship by the Society for Healthcare Epidemiology of America (SHEA), the Infectious Diseases Society of America (IDSA), and the Pediatric Infectious Diseases Society (PIDS). *Infection Control & Hospital Epidemiology,*.

Flannery, D. D. (2014). Prescriber perceptions of a pediatric antimicrobial stewardship program.

Fuchs, A. B. (2018). eviewing the WHO guidelines for antibiotic use for sepsis in neonates and children. .

Gagliotti, C. M. (2006). Antibiotic treatments for children ages 0–23 months in a northern Italy region: a cohort study.

Gerber, J. S. (2010). Variability in antibiotic use at children's hospitals. *Pediatrics,*.

Gerber, J. S. (2010). Variability in antibiotic use at children's hospitals.

Gerber, J. S. (2013). Identifying targets for antimicrobial stewardship in children's hospitals.

Goff, D. A. (2017). A global call from five countries to collaborate in antibiotic stewardship: united we succeed, divided we might fail.

Graham, S. M. (2006). Low levels of pyrazinamide and ethambutol in children with tuberculosis and impact of age, nutritional status, and human immunodeficiency virus infection. *Antimicrobial agents and chemotherapy*.

Gül, H. C. (2013). Antibiotic usage and appropriateness at a university hospital in Turkey: point prevalence results. *Nobel Med,* .

Haaijer-Ruskamp, F. M. (1996). New approaches to influencing physicians' drug choices: the practice-based strategy. *Oxford University Press, New York/Oxford,*.

Hardin, A. P. (2017). Age limit of pediatrics. *Pediatrics*.

Hazards, E. P. (2009). Joint Opinion on antimicrobial resistance (AMR) focused on zoonotic infections. *EFSA Journal, 7(11), 1372.*

Henderson, F. W. (1988). Nasopharyngeal carriage of antibiotic-resistant pneumococci by children in group day care.

Hersh, A. L. (2011). Antibiotic prescribing in ambulatory pediatrics in the United States. *Pediatrics*.

Hersh, A. L. (2011). Antibiotic prescribing in ambulatory pediatrics in the United States. *Pediatrics*.

Hockenberry, M. J. (2013). Wong's Essentials of Pediatric Nursing9: Wong's Essentials of Pediatric Nursing. *Elsevier Health Sciences.*

Hogerzeil, H. S. (1989). mpact of an essential drugs programme on availability and rational use of drugs.

Holloway, K. &. (2011). Rational use of medicines.

Holloway, K. A. (2011). Promoting the rational use of antibiotics. *Reg. Health Forum*.

Huttunen, J. T. (2003). Methane emissions from natural peatlands in the northern boreal zone in Finland, Fennoscandia. . *Atmospheric Environment*.

J, K. (2006). British National Formulary for Children 2005. *uality & Safety in Health Care*.

Jalanko, H. (2014). Flunssa lapsella. Duodecim.

James, L. P. (1998). Pharmacokinetics and pharmacodynamics of famotidine in infants.

Johnson TN, T. M. (2008). Intestinal metabolism and transport of drugs in children: the effects of age and disease.

Kalliola, S. (2015). Airway Responsiveness and Inflammation in Young Children with Respiratory Symptoms.

Kaplan, W. W. (2013). Priority Medicines for Europe and the World Update 2013 report.

Karim, R. R. (2004). Community pharmacists' knowledge and dispensing recommendations for treatment of acute diarrhoea in Trinidad, West Indies. *International journal of clinical practice, 58(3), 264-267*.

Katakam, P. E. (2012). A retrospective study on antibiotic use in different clinical departments of a teaching hospital in Zawiya, Libya.

Kearns, G. L.-R. (2003). Developmental pharmacology—drug disposition, action, and therapy in infants and children.

Kearns, G. L.-R. (2003). Developmental pharmacology—drug disposition, action, and therapy in infants and children. *New England Journal of Medicine,*.

Kim, B. N. (2005). Compliance with an infectious disease specialist's advisory consultations on targeted antibiotic usage. . *Journal of infection and chemotherapy, 11(2), 84-88*.

Kocak, I. Ü. (2005). Prophylactic antibiotics in elective abdominal hysterectomy. *International Journal of Gynecology & Obstetrics,*.

Kompare, M. &. (2012). Protracted Bacterial Bronchitis in Young Children: Association with Airway Malacia. *The Journal of Pediatrics*.

Korppi, M. T.-J.-M. (2015). Alahengitystieinfektiot.

Kunin, C. M. (1987). Social, behavioral, and practical factors affecting antibiotic use worldwide: report of Task Force 4. *Reviews of infectious diseases,* .

Le Grand, A. H.-R. (1999). Intervention research in rational use of drugs: a review. Health policy and planning,. *Health policy and planning*.

Le Grand, A. H.-R. (1999). Intervention research in rational use of drugs: a review.

Leekha, S. T. (2011). General principles of antimicrobial therapy. In Mayo Clinic Proceedings . *Elsevier*.

Levy, E. R. (2012). Rates and appropriateness of antimicrobial prescribing at an academic children's hospital, 2007–2010. *Infection Control & Hospital Epidemiology, 33(4), 346-353.*

Levy, E. R. (2012). Rates and appropriateness of antimicrobial prescribing at an academic children's hospital, 2007–2010.

Levy, E. R. (2012). Rates and appropriateness of antimicrobial prescribing at an academic children's hospital, 2007–2010. *Infection Control & Hospital Epidemiology,*.

Levy, M. M. (2014). Surviving Sepsis Campaign: association between performance metrics and outcomes in a 7.5-year study. *Intensive care medicine*.

Lim, V. K. (1993). Pattern of antibiotic usage in hospitals in Malaysia. *Singapore medical journal,*.

Lumio, J. (2013). Infektioiden aiheuttajat: loiset, bakteerit, sienet, alkueläimet, virukset ja prionit.

MacDougall, C. &. (2005). Antimicrobial stewardship programs in health care systems.

McCaig, L. F. (1995). Trends in antimicrobial drug prescribing among office-based physicians in the United States.

McCaig, L. F. (2003). Antimicrobial-drug prescription in ambulatory care settings, United States, 1992–2000. *Emerging infectious diseases,*.

McNulty, C. A. (2012). Education of healthcare professionals and the public. .

Metjian, T. A. (2008). Evaluation of an antimicrobial stewardship program at a pediatric teaching hospital.

Morley, P. S.-C. (2005). ntimicrobial drug use in veterinary medicine. *Journal of veterinary internal medicine,* .

Morselli PL, P. C. (1983). Antiepileptic drug therapy in pediatrics.

Mousavi, S. B. (2013). Drug utilization evaluation of imipenem and intravenous ciprofloxacin in a teaching hospita.

Nash, D. R. (2002). Antibiotic prescribing by primary care physicians for children with upper respiratory tract infections. *Archives of pediatrics & adolescent medicine, 156(11), 1114-1119.*

Nash, D. R. (2002). Antibiotic prescribing by primary care physicians for children with upper respiratory tract infections. *Archives of pediatrics & adolescent medicine*.

Nathwani, D. D. (1996). Impact of an infection consultation service for bacteraemia on clinical management and use of resources. *An International Journal of Medicine*.

Nausheen, S. H. (2013). Rational use of antibiotics--a quality improvement initiative in hospital setting. *ournal Pakistan Medical Association,*.

Neubert, A. S. (2008). Databases for pediatric medicine research in Europe—assessment and critical appraisal. *Pharmacoepidemiology and drug safety, 17(12), 1155-1167.*

Newland, J. G. (2014). revalence and characteristics of antimicrobial stewardship programs at freestanding children's hospitals in the United States.

Niederman, M. S. (2005). Principles of appropriate antibiotic use. *nternational journal of antimicrobial agents,*.

Noterman, H. &. (2016). nfectious diseases in children and treatment at home: guidebook for parents.

Nyquist, A. C. (1998). Antibiotic prescribing for children with colds, upper respiratory tract infections, and bronchitis.

Ochoa, C. E. (2000). Assessment of antibiotic prescription in acute respiratory infections in adults.

Organization, W. H. (2003). Introduction to drug utilization research. *World Health Organization.*

Porta, A. H. (2012). Comparing neonatal and paediatric antibiotic prescribing between hospitals: a new algorithm to help international benchmarking. *Journal of antimicrobial chemotherapy, 67(5), 1278-1286*.

Quick, J. D.-D. (1991). Intervention research to promote clinically effective and economically efficient use of pharmaceuticals: the International Network for Rational Use of Drugs. *Journal of clinical epidemiology,*.

Quick, J. D.-D. (1991). Intervention research to promote clinically effective and economically efficient use of pharmaceuticals: the International Network for Rational Use of Drugs.

Radyowijati, A. &. (2003). *Improving antibiotic use in low-income countries: an overview of evidence on determinants.* Social science & medicine, 57(4), 733-744.

Rajantie, J. M. (2010). Lastentaudit.

Resistance., R. o. (2015). Antimicrobials in agriculture and the environment: reducing unnecessary use and waste. *Review on Antimicrobial Resistance*.

RN, H. (2008). The ontogeny of drug metabolism enzymes and implications for adverse drug events.

Salehifar, E. N. (2014). Determination of antibiotics consumption in Buali-Sina pediatric Hospital, Sari 2010-2011. *Iranian journal of pharmaceutical research:*.

Schentag, J. J. (1993). Changes in antimicrobial agent usage resulting from interactions among clinical pharmacy, the infectious disease division, and the microbiology laboratory. *Diagnostic microbiology and infectious disease*.

Schindler, C. K. (2003). Prescriptions of systemic antibiotics for children in Germany aged between 0 and 6 years.

Sharma, M. D. (2015). Antibiotic prescribing among pediatric inpatients with potential infections in two private sector hospitals in Central India. *PLoS One,*.

Siimes, M. &. (2015). Burden of Influenza in Children.

Skjerven, H. M. (2015). Virus Type and Genomic Load in Acute Bronchiolitis: Severity and Treatment Responce With Inhaled Adrenaline. *The Journal of Infectious Diseases.*

Slama, T. G. (2005). A clinician's guide to the appropriate and accurate use of antibiotics: the Council for Appropriate and Rational Antibiotic Therapy (CARAT) criteria.

Smith, M. J. (2015). npatient antimicrobial stewardship in pediatrics: a systematic review.

Smith, M. J. (2015). npatient antimicrobial stewardship in pediatrics: a systematic review. .

Society, A. T. (1993). Guidelines for the initial management of adults with community-acquired pneumonia: diagnosis, assessment of severity, and initial antimicrobial therapy.

Spyridis, N. S. (2016). Variation in paediatric hospital antibiotic guidelines in Europe. *rchives of disease in childhood, 101(1), 72-76.*

Star, K. C. (2011). Dose Variations Associated with Formulations of NSAID Prescriptions for Children. *Drug safety, 34(4), 307-317.*

Sviestina, I. &. (2018). Observational Study of Antibiotic Usage at the Children's Clinical University Hospital in Riga, Latvia.

Tornimbene, B. E.-S. (2018). WHO Global Antimicrobial Resistance Surveillance System early implementation 2016–17.

US FDA. (2013). Guidance for Industry.

Versporten, A. B. (2016). The Worldwide Antibiotic Resistance and Prescribing in European Children (ARPEC) point prevalence survey: developing hospital-quality indicators of antibiotic prescribing for children. *Journal of Antimicrobial Chemotherapy, 71(4), 1106-1117.*

Wells, B. G. (2015). Pharmacotherapy handbook. C. V. DiPiro.

WHO. (1977). nternational Classification of Diseases: Manual of the International Statistical Classification of Diseases.

who. (1987). WHO Regional Office for Europe: List of Documents1951-1982: Revision 2: August 1987.

WHO. (2002). WHO fact sheet no. 194, revised January 2002.

WHO. (2003). Drug and therapeutics committees: a practical guide .

WHO. (2007). Paediatric Age Categories to be Used in Differentiating Between Listing on a Model Essential Medicines List for Children.

WHO. (2013). Technical consultation: strategies for global surveillance of antimicrobial resistance, 8-19 December 2012 World Health Organization Headquarters,. *Geneva: meeting report (No. WHO/HSE/PED/2013.10358). World Health Organization.*

WHO. (2016). iftieth report of the WHO Expert Committee on specifications for pharmaceutical preparations.

YILMAZ, G. R. (2009). Examining antibiotic use at an education and research hospital in Turkey: point prevalence results. *Turkish Journal of Medical Sciences,*.

CURRICULUM VITAE:

Name	**NOUR**	Surname	**AL Kharrat**
Place of birth	Syria	Date of birth	1 -1- 1992
Nationality	Syrian	Tel	00963938969412
Email	noorkharrat@gmail.com		

Education Level

	Name of the Institution where he/she was graduated	Graduation year
Postgraduate/ Specialization	-	_
Masters	NEU	2019
Undergraduate	International University for Science and Technology(IUST)	2016
High school	Abdulkader Mubarak	2009

Job experience

Duty	Institution	Duration (Year-Year)
Pharmacist	Al Sham pharmacy	2016-2017
Teacher	Al shams Al mushreqa school	2012-2013

Foreign Language	Reading Comprehension	Speaking	Writing
Arabic	Very good	Very good	Very good
English	Very good	Very good	Very good
French	good	good	good

Foreign Language Examination Grade

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

	Math	Equally weighted	Non-math
ALES Grade	-	-	-
Other grade	-	-	-

Computer Knowledge

Program	Use proficiency
ICDL	Very good

ENCLOSURE: Other scientific activities (publication, congress proceedings etc.)