TURKISH REPUBLIC OF NORTH CYPRUS

NEAR EAST UNIVERSITY

HEALTH SCIENCES INSTITUTE

ANTIBIOTIC UTILIZATION PATTERNS IN INTENSIVE CARE UNIT AT NEAR EAST UNIVERSITY HOSPITAL

ALAA ALMANSOUR

MASTER THESIS

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

CLINICAL PHARMACY

Supervisor:

Assoc. Prof. Dr. ABDIKARIM ABDI

Northern Cyprus, Nicosia

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THESIS APPROVAL

Directorate of Institute of Health Sciences

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.

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NEAR EAST UNIVERSITY GRADUATE SCHOOL OF HEALTH SCIENCES, NICOSIA 2020

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☐ Master's without Thesis ☐ Master's with Thesis ☐ Doctorate

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....
(Signature)

DEDICATION

I am grateful to Allah for having so many blessings.

This thesis is dedicated to my parents ***Ziad Almansour and Nadia*** *who* have 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 son ***Malek*** who inspired me to do what I meant to do.

ACKNOWLEDGMENTS

I owe my sincerest gratitude and much respect to my adviser and mentor, Assoc. Prof. Dr. Abdikarim Abdi, for his remarkable support, advice, and words of encouragement throughout the steps of this work.

I am grateful to Prof. Bilgen Basgut, the Head of the Clinical pharmacy department at Near East University, for her teaching, her time with us and support that she gave me during my study.

I am thankful to Prof. Dr. Kaya Süer, Prof. Dr. Nedim Çakir, for their advice and support.

I am thankful to my family members, father Ziad Almansour, mother: Nadia, brothers: Mohammed, Ali and Omar, sisters; Elaf and Mariam whose support, prayers, and trust are the great factors that push me forward to acquire success.

TABLE OF CONTENTS

LIST OF TABLES

Page No

LIST OF FIGURE

LIST OF ABBREVIATIONS

ADR	:Adverse drug reactions
AMR	:Antimicrobial resistance
AST	:Antibacterial susceptibility test
CAP	:Community acquired pneumonia
CAUTI	:Catheter-associated Urinary Tract Infections
CDC	:Centre for disease control and prevention
CDIs	:Clostridium difficult infections
CLABSI	:Central Line-associated Bloodstream Infection
CRP	:C-reactive protein
DDD	:Defined Daily Dose
DGIM	:The German Society of Internal Medicine
DOD	:Days
DUE	:Drug Use Evaluation
ECDC	:European center for disease control and preventions
ESR	:Erythrocyte sedimentation rate
HAIs	:Hospital acquired infections
HAP	:Hospital acquired pneumonia
HCAIs	:Health care associated infections
LOS	:length of stay
ICU	:Intensive care unit
IV	:Intravenous

PCT	:Procalcitonin
PD	:Pharmacodynamics
PK	:Pharmacokinetics
PS	:Prevalence survey
SPSS	:Statistical Package for Social Sciences software
SSI	:Surgical Site Infection
VAP	:Ventilator Associated Pneumonia
WHO	:World health organization

Disease ICD codes

Diseases	**ICD code**
PNOMONIA	J15.0
COPD	Y93
CANCER	D70.1
SEPTIC SHOCK	R56.21
COMA	R 40.2
SEIZURE	G40.5
CARDIAC DISEASE	P35.4
BARAIN SURGERY	I97.120
SEPSIS	T81.44

Antibiotic Utilization Patterns in Intensive Care Unit at Near East University Hospital

Name of the student: Alaa Almansour

Mentor: Assoc. Prof. Dr. Abdikarim Abdi

Department: Clinical Pharmacy

ABSTRACT

The overuse of antibiotics all over the world has becomes a concern. This overuse especially in the intensive care unit gives rise to drug resistance in microbes that lead to drug-resistant bacterial infections. The damage that has already been done must be reversed, and additional resistance prevented.

This research investigates the reasons leading to the over-use and misuse of antibiotics by health care providers. Raising awareness about the irrational Antibiotics utilization and its consequences in increasing bacterial resistance; that contributes to an increase in the length of stay (LOS), morbidity, and mortality.

Aim: The study aims to evaluate Antibiotic utilization in the critically ill patient who has admitted to the intensive care unit in Near East University Hospital. Based on finding recommendations will be established to prevent and control the irrational use of antibiotics.

Method: The study design is a retrospective study in the archives of the Near east university hospital (NEUH) **(1-January,2016 of 31-December 2019**) to find the Antibiotic related problem (the rationality of antibiotics used) in the ICU.

The inclusion criteria: All patients aged >18 years. And only patients admitted to ICU who received at least one Antibiotic. The excluded criteria: Patients with an incomplete file will exclude Patients who did not receive antibiotics.

The antibiogram will be done retrospective according to WHO guidelines and IDSA guidelines) from 1-January 2019 to 31-December 2019. As a local guideline.

Result: There were 522 patients admitted to ICU between 1st, Jan. 2016 and 31st, Dec. 2019, 352 patients were including in the analysis. There were 168(47.7%) females and 184(52.3%) males with average age 70.88 years, SD (±16.297), 208 (59.1%0) patients were ventilated and 144 (40.9%) were did not use the ventilator. The none geriatric population was 105 (29.9%) and the geriatric population was 246(70.1%). The total mortality rate was out of 228 (84.6%). There were 244(69.5%) patients who receive irrational antibiotics while 107(30.5%) patients receive a rational antibiotic. Out of 352, there were 162(46.2%) patients admitted due to respiratory disorder follow by110 (31.3%) anesthesia while the lowest cause of admission was neurology disease. Data show the most used antibiotic is Meropenem 144(41%) followed by Piperacillin-tazobactam 139(39.6%) then Ciprofloxacin 98(27.90%).

The data showed that the staying period for the rational drug used patients was significantly lower than irrational. (8.6±9.0) (18.7±25.5) ($p<0.005$) respectively. A regression test of mortality shows that Is associated with MDR development $p<0.05$ and also with an increase in PCT $p<0.05$

Conclusion:

In conclusion, the result obtained from our study shows that the rate of irrational antibiotic is high, especially with patients who need dose adjustment, de-escalation of antibiotic to narrower spectrum is a major problem, as the" time-out "concept is not applied in our hospital.

High consumption of broad-spectrum antibiotics for a long time associated with nosocomial infection, MDR development which leads to an increase in LOS and mortality.

Poor documentation for the antibiotic selection, the dose, the administration instruction, and the duration are considering another concern should be aware to avoid and control most of the problem.

Yakın Doğu Üniversitesi Hastanesi Yoğun Bakım Ünitesinde Antibiyotik Kullanım Şekilleri

Öğrencinin adı: Alaa Almansour

Danışman: Doç. Abdikarim Abdi

Bölüm: Klinik Eczacılık

ÖZ

Tüm dünyada antibiyotiklerin aşırı kullanımı endişe kaynağı haline geldi. Özellikle yoğun bakım ünitesindeki bu aşırı kullanım, ilaca dirençli bakteriyel enfeksiyonlara yol açan mikroplarda ilaç direncine yol açar. Daha önce yapılmış olan hasar tersine çevrilmeli ve ek direnç önlenmelidir.

Bu araştırma, sağlık hizmeti sunanlar tarafından antibiyotiklerin aşırı kullanımına ve kötüye kullanılmasına neden olan nedenleri araştırmaktadır. İrrasyonel Antibiyotik kullanımı ve bakteri direncini arttırmadaki sonuçları hakkında farkındalık yaratmak; kalış süresi (LOS), morbidite ve mortalitede artışa katkıda bulunur.

Amaç: Bu çalışma Yakın Doğu Üniversitesi Hastanesi'nde yoğun bakım ünitesine başvuran kritik hastadaki Antibiyotik kullanımını değerlendirmeyi amaçlamaktadır. Bulgulara dayanarak, antibiyotiklerin irrasyonel kullanımını önlemek ve kontrol etmek için öneriler oluşturulacaktır.

Yöntem: Çalışma tasarımı YBÜ'de Antibiyotikle ilgili sorunu (kullanılan antibiyotiklerin rasyonalitesi) bulmak için Yakın Doğu Üniversitesi Hastanesi (NEUH) arşivlerinde (1-Ocak, 31-Aralık 2019) geriye dönük bir çalışmadır.

Kapsama alınan kriterler: 18 yaşın üzerindeki tüm hastalar. Ve sadece YBÜ'ye en az bir Antibiyotik alan hastalar başvurdu. Hariç tutulan ölçütler: Eksik bir dosyaya sahip olan hastalar antibiyotik almayan Hastaları hariç tutacaktır.

Antibiyogram 1 Ocak 2019 ile 31 Aralık 2019 tarihleri arasında DSÖ kılavuzlarına ve IDSA kılavuzlarına göre geriye dönük olarak yapılacaktır. Yerel bir kılavuz olarak.

Sonuç: 1 Ocak 2016 ile 31 Aralık 2019 tarihleri arasında yoğun bakım ünitesine başvuran 522 hasta vardı, 352 hasta analize dahil edildi. Yaş ortalaması 70.88 olan 168 (% 47.7) kadın ve 184 (% 52.3) erkek, SD (± 16.297), 208 (% 59.1 0) hasta havalandırıldı ve 144 (% 40.9) ventilatör kullanılmadı. Geriatrik olmayan popülasyon 105 (% 29.9) ve geriatrik popülasyon 246 (% 70.1) idi. Toplam ölüm oranı 228'den (% 84.6) çıktı. İrrasyonel antibiyotik kullanan 244 (% 69.5) hasta, 107 (% 30.5) hastaya rasyonel antibiyotik verildi. 352 hastadan 162'si (% 46.2) solunum bozukluğu nedeniyle başvurdu110 (% 31.3) anestezi takip ederken en düşük başvuru nedeni nöroloji hastalığı idi. Veriler en çok kullanılan antibiyotiğin Meropenem 144 (% 41) ve ardından Piperasilin-tazobaktam 139 (% 39.6), sonra Ciprofloksasin 98 (% 27.90) olduğunu göstermektedir.

Veriler, rasyonel ilaç kullanılan hastalarda kalma süresinin irrasyonelden anlamlı derecede düşük olduğunu gösterdi. (8.6 ± 9.0) (18.7 ± 25.5) ($p < 0.005$). Bir regresyon mortalite testi, MDR gelişimi ile ilişkili olduğunu gösterir $p < 0.05$ ve ayrıca PCT'de bir artış ile $p < 0.05$

Sonuç:

Sonuç olarak, çalışmamızdan elde edilen sonuç irrasyonel antibiyotik oranının yüksek olduğunu göstermektedir, özellikle doz ayarlaması gereken hastalarda, antibiyotiğin daha dar spektruma yükselmesi önemli bir sorundur, çünkü “zaman aşımı” kavramı hastanemize başvurdu.

Nozokomiyal enfeksiyon, LOS ve mortalitede artışa neden olan MDR gelişimi ile ilişkili uzun süre geniş spektrumlu antibiyotik tüketimi.

Antibiyotik seçimi, doz, uygulama talimatı ve süre için yetersiz dokümantasyon, sorunun çoğunu önlemek ve kontrol etmek için başka bir endişe olduğunu düşünüyor.

1. INTRODUCTION

1.1 Back Ground and Aim

Severe disease induces and complicates infection. In the intensive care unit (Rodríguez-Acelas et al. 2017), the highest levels of nosocomial infection occur with an average incidence ranging between 10 to 45% of total admissions to the ICU (Masnoon et al. 2018). Pneumonia linked to a ventilator forms 10–15% of ICU patients (Vestjens et al. 2018). While nosocomial bloodstream and urine infections are comparatively less common (Abram et al. 2020). ICU-acquired infections are estimated to increase the cost of hospitalization by two-fold. Risk factors include length of stay, patient age and gender, surgery since admission, hospital setting, invasive devices usage i.e. in neurological injury, and previous use of antibiotics. It is notoriously difficult to diagnose ICU-acquired infection. Infection is difficult to tell; the difference between clinical and laboratory manifestations and colonization, and the concomitant usage of antibiotics can make culture unlikely (Guanche-Garcell et al. 2011).

Infection linked to healthcare (HAI) is one of the world's leading issues. These are the most prevalent infections among patients with significant involvement, fire, insufficiency of the liver, cancer, metabolism or transplant. About 1.7 million patients per year produce HAIs in the U.S(Klevens et al. 2007). Four times higher rate of patient mortality is attributed to nosocomial infections, while such infection are associated with 3 times longer duration of stay in hospitals (Roberts et al. 2010). Patients in intensive care units (ICUs) are one of the major target populations for hospital pathogens. ICU-acquired infections constitute about half of all HAIs (Vincent 2003). The mortality rates and morbidity due to extensively antimicrobial resistant pathogens further complicate the critical condition of the patients in the ICU (Guducuoglu et al. 2018).

Therefore, it is important to track ICU pathogens and record their AMR to ensure that the preventive, control and therapeutic action measures are planned efficiently. Drug used evaluation strategies should be followed by clinical pharmacist as a study in Norway evaluate the impact of clinical pharmacist (Johansen et al. 2016), unlike the role of pharmacist in North Cyprus which is only for dispensing drug (Abdi et al. 2018). This study aims to evaluate Antibiotic utilization in the critically ill patient who has admitted to the intensive care unit in Near East University Hospital. Based on finding recommendations will be established to prevent and control the irrational use of antibiotics.

2. LITERATURE REVIEW

2.1. Overview of Health Care System

In the face of different economic, political, cultural, environmental, epidemiologic, and demographic forces, each country tries to tailor its health care system to the specific characteristics and needs. They need ways to evaluate treatments and health care interventions and approaches to disseminate them. They need ways to educate clinicians about health and medicine, as well as ways to educate everyone else, help their populations lead healthy lives, make wise health care decisions, and participate in their care. With healthcare costs ranging from about 2% to more than 17% of GDP, they need ways to pay for it all (Morrissey et al. 2015).

In truth, most effective national healthcare systems have had both successes and failures and have continued to shift and change, whether through reasoned evolution or owing to the swing of a political or economic pendulum. Some national health policymakers may find surprisingly applicable approaches in countries whose cultural and political assumptions differ markedly from their own. Even struggling healthcare systems may have a few hidden gems that can inspire broadly productive changes (Morrissey et al. 2015).

2.1.1. Health Care System in Turkey

Turkey has accomplished remarkable improvements in health status in the last three decades, particularly after the implementation of the Health Transformation Program HTP. The leading causes of death are diseases of the circulatory system, followed by malignant neoplasms. Turkey's healthcare system has been undergoing a far-reaching reform process since 2003, and radical changes have occurred in the provision and financing of health care services. Health services are now financed through a social security scheme covering the majority of the population, the General Health Insurance Scheme GHIS, and services are provided both by public and private sector facilities (Tatar et al. 2011) (Bener et al. 2019).

The Social Security Institution SSI, financed through payments by employers and employees and government contributions in cases of the budget deficit, has become a monopsony power on the purchasing side of health care services. On the provision side, the Ministry of Health is the main actor and provides primary, secondary, and tertiary care through its facilities.(Tatar et al. 2011).

Over the last ten years, the Turkish has dramatically improved and strengthened. Yet, far from perfect, plans are to improve further involving the enrollment of highly trained personnel. More precise and dependable information from hospitals and PHC centers in Turkey needs to be obtained urgently to aid also help infrequently assessing and monitoring healthcare quality in the context of services and processes (Bener et al. 2019).

2.1.2. Health care system in Cyprus

The island of Cyprus is divided into two parts. While the Republic of Cyprus has prospered, becoming a member of the European Union in 2004, Northern Cyprus has remained under economic sanctions and has been left relatively isolated from the rest of the world for nearly 40 years. (Rahmioglu, Naci, and Cylus 2012).

Consequently, high out-of-pocket health care expenditures are extremely common. Cyprus government has a formal scheme, sending individuals free of charge to Turkey for specialist health care if the required services are not available specifically within the public sector. A total of 2023 patients were sent to Turkey in 2010, most commonly for cardiovascular disease and cancer treatment. The fourth care pathway is by crossing the border and receiving public services in the Republic of Cyprus (Rahmioglu, Naci, and Cylus 2012).

The health care system in the Republic of Cyprus comprises comparably sized public and private sectors, which exist in parallel. In an attempt to address these issues, the Republic of Cyprus has worked towards implementation of a national health insurance scheme, which is designed to provide universal coverage by introducing competition between the public and private sectors, adding a social insurance component to financing and changing the way providers are paid (Rahmioglu, Naci, and Cylus 2012).

2.1.3. Patient Care in ICU

During the Crimean War in 1854, Florence Nightingale and a team of nurses created an area of the military field hospital that could provide more intensive nursing care for the most severely injured soldiers (Marshall et al. 2017).

In Copenhagen Municipal Hospital in December 1953, the first multidisciplinary intensive care unit in the world was created. The Danish anesthesiologist Bjørn Ibsen (born: 1915) was responsible for the definition. The paper sets out the conditions which enabled Ibsen to set up a unit to monitor and treated all categories of severely ill patients around the clock in line with the operating theatres. The history of the development of technology and science in intensive therapy is summarized shortly. The inference is that while intensive care therapy is increasingly advanced, it still has a weakness because it begins too late. We must establish an early alert network (Berthelsen 2007) (Kelly et al. 2014).

Intensive care units were established in France in 1954 (Vachon 2011) , in Baltimore in 1957 , and Toronto in the late 1950s as discrete geographic areas within the hospital that brought together developing technologies for organ support such as positive pressure ventilation, hemodialysis, and invasive cardiovascular monitoring (Rood 1988).

The World Federation of Societies of Intensive and Critical Care Medicine (WFSICCM) – a federation of close to 80 professional societies representing the clinicians from around the world who care for critically ill patients – struck a task force whose remit was to develop a globally applicable answer to the question, “What is an Intensive Care Unit?”.

Intensive care continues to evolve, from a specialty defined by a discrete area of the hospital to one defined more broadly by the capacity to provide rapid resuscitative and supportive care where it is needed – on the hospital ward by dedicated outreach teams, in the emergency department, and even in the pre-hospital setting (Williams and Wheeler 2009)(Marshall et al. 2017).

Patients who are with serious diseases, or acute impairment of one or more organ systems who also require support for an acute reversible failure of another organ or requiring advanced respiratory support; those patients have a significant risk of acquiring infections related to healthcare (Despotovic et al. 2020). Nosocomial infections that are device-related are considered a standard threat to a patient's wellbeing in the intensive care unit and are considered to be a cause of patient morbidity and mortality (Williams and Wheeler, 2009) . The use of invasive devices is a danger to the safety of each patient and a potential health risk for patients because it increases the possibility of these patients acquiring a HA I (Vanhems et al. 2011) .These types of infections can be linked with extended hospital stays, sustained costs, and correlated with higher number of comorbidities.(Williams and Wheeler 2009)(Gonzalez Del Castillo et al. 2019).

2.2. General Concept regarding Infectious Diseases

Infectious disease, in medicine, a process caused by an agent, often a type of microorganism, that impairs a person's health. In many cases, an infectious disease can be spread from person to person, either directly or indirectly. When health is not altered, the process is called subclinical infection. Thus, a person may be infected but not have an infectious disease (Lowy, 1890).

This principle is illustrated by the use of vaccines for the prevention of infectious diseases. The immunization is designed to produce a measles infection in the recipient but generally causes no discernible alteration in the state of health. When these issues have been broken or affected by the earlier disease, invasion by infectious agents may occur. These infectious agents may produce a local infectious disease, such as boils, or may invade the bloodstream and be carried throughout the body, producing generalized bloodstream infection or localized infection at a distant site, such as meningitis (Who 2012b)(Shane et al. 2017).

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Bacteria can survive within the body but outside individual cells. Some bacteria, classified as aerobes, require oxygen for growth, while others, such as those normally found in the small intestine of healthy persons, grow only in the absence of oxygen and, therefore, are called anaerobes. Most bacteria are surrounded by a capsule that appears to play an important role in their ability to produce disease. Bacteria are generally large enough to be seen under a light microscope (Lewis, 2005).

Streptococci, the bacteria that cause scarlet fever, is about 0.75 micrometers in diameter. The spirochetes, which cause syphilis, leptospirosis, and rat-bite fever, are 5 to 15 micrometers long. Bacterial infections can be treated with antibiotics. Bacterial infections are commonly caused by pneumococci, staphylococci, and streptococci, all of which are often commensals in the upper respiratory tract but that can become virulent and cause serious conditions, such as pneumonia, septicemia, and meningitis (Weiser, Ferreira, and Paton 2018) (M. Ramirez et al. 2015).

The pneumococcus is the most common cause of lobar pneumonia, the disease in which one or more lobes, or segments, of the lung, become solid and airless as a result of inflammation. Streptococcal pneumonia is the least common of the three and occurs usually as a complication of influenza or other lung diseases. Pneumococci often enter the bloodstream from inflamed lungs and cause septicemia, with continued fever but no other special symptoms. In the course of either of the last two forms of septicemia, organisms may enter the nervous system and cause streptococcal or staphylococcal meningitis, but these are rare conditions(Kwun et al. 2019)(Henriques-Normark and Tuomanen, 2013).

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Pneumococci, on the other hand, often spread directly into the central nervous system, causing one of the common forms of meningitis. Staphylococci and streptococci are common causes of skin diseases. Streptococci can be the cause of the red cellulitis of the skin known as erysipelas. Some staphylococci produce an intestinal toxin and cause food poisoning (Echchannaoui et al. 2002) (Engelen-Lee et al. 2016).

Certain streptococci settling in the throat produce a reddening toxin that speeds through the bloodstream and produces the symptoms of scarlet fever. Streptococci and staphylococci also can cause toxic shock syndrome, a potentially fatal disease(Yumoto et al. 2019)(Junges et al. 2019).

Meningococcal meningitis, at one time a dreaded and still a very serious disease, usually responds to treatment with penicillin if diagnosed early enough. When meningococci invade the bloodstream, some gain access to the skin and cause bloodstained spots or purpura. If the condition is diagnosed early enough, antibiotics can clear the bloodstream of the bacterium and prevent any from getting far enough to cause meningitis. The diagnosis is established by cultures of blood, cerebrospinal fluid, or other tissue from sites of infection (Van De Beek et al. 2016) (Hayashi et al. 2017). Antibiotic therapy is generally effective, although death from sepsis or meningitis is still common. influenza vaccine is used, there has been a great decrease in serious infections and deaths (Hayashi et al. 2017).

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Chlamydial organisms; can produce eye and pneumonia disease in the newborn when an infant pass through an infected birth canal. Young children sometimes develop ear infections, laryngitis, and upper respiratory tract disease from Chlamydia. The illness is characterized by high fever with chills, a slow heart rate, pneumonia, headache, weakness, fatigue, muscle pains, anorexia, nausea, and vomiting (Hokynar et al. 2016).

Viruses are not considered living organisms. Instead, they are nucleic acid fragments packaged within protein coats that require the machinery of living cells to replicate. Viruses of the Herpesviridae family cause a multiplicity of diseases. There are two serotypes of herpes simplex virus, HSV-1 and HSV-2(Tang et al. 2017).

Fungi may exist as yeasts or molds and may alternate between the two forms, depending on environmental conditions. These diseases can be mild, characterized by an upper respiratory infection, or severe, involving the bloodstream and every organ system. Fungi may cause devastating disease in persons whose defenses against infection have been weakened by malnutrition, cancer, or the use of immunosuppressive drugs (Basenko et al. 2018).

2.3 Infectious Diseases In ICU

2.3.1 CDC highlights the following four infectious diseases related to ICU devices. They work on the monitor and prevent them as they are threatening patient safety("Check List" 2013)

1. ***Central Line-associated Bloodstream Infection (CLABSI):***. The critically ill patient needs a central line catheter-that placed near the heart to obtain parenteral nutrition, medication, and other fluid they required. However, the inappropriate indwelling of this catheter leads to develop an infection within 48 hours. This infection leads to increase patient complications, LOS, cost, and of course, mortality (Guanche-Garcell et al. 2011) (Pliakos et al. 2019). The Medical Institute reported that medical errors caused up to 98 000 deaths/year. 50% of the time, the care required is increased. These medical complications CLABSI, contribute to morbidity and lead to a rise to the extent of disease. The length of the stay in healthcare health costs and mortality (DePalo et al. 2010). National Safety Network for Healthcare Info, also reported that 85 994 In the United States, CLABSI cases have been reported in the years 2011-14. CLABSI are significantly linked to high death levels, lengthy hospital stays, and an annual $45,814 per episode in the average cost (Pliakos et al. 2019) (Zimlichman et al. 2013). A study conducted in Europe showed that applying guidelines in implanting the catheter has an impact on reducing morbidity and mortality and the treatment choice (Schreiber et al. 2019). Empiric antibiotics start as soon as

possible, but AB's choice must be carefully made to avoid treatment failure and the development of multidrug resistance organisms (MDR)(Pliakos et al. 2019).

2. ***<u>Catheter-associated Urinary Tract Infections (CAUTI)</u>:*** The 5th most common form of infection associated with health care, with about 62,700 UTIs in acute care hospitals in 2015, are urinary tract infections (UTIs). UTIs additionally cause more than 9,5% of infections reported by acute care hospitals. Virtually all health-associated UTIs arise from urinary tract instrumentation. (CDC 2020)

   CAUTI that remains for a long time associated with infection. These infections can lead to additional complications, including cystitis, pyelonephritis, prostatitis, bacteremia, epididymis, etc. Diabetes, renal disease, and structural abnormalities are complicating CAUTIs that affect urine flow. Around half of all nosocomial infections have been estimated to be caused by CAUTIs. CAUTIs in the United States are among the most popular HAIs and can be prevented (Mody et al. 2017).

3. ***<u>Surgical site infections (SSI</u>***), Which occur after surgery, are incision infections or organ or space infections. SSI prevention is becoming increasingly relevant, as the number of surgery procedures carried out in the United States continues to grow. Around half of SSIs have been calculated to be preventable by applying evidence-based strategies. As a consequence, surgical patients who have initially been diagnosed with more complex co-morbidities and the emergence of anti-microbial-resistant pathogens increase costs and challenges for the treatment of SSI (Berriós-Torres et al. 2017) (Onyekwelu et al. 2017).

4. ***<u>Pneumonia:</u>*** Community acquired pneumonia (CAP) is commonly caused by bacterial infection, and consider the most common cause of admission to intensive care (Kollef et al. 2017). Hospital-acquired pneumonia (HAP) and ventilated associated pneumonia (VAP) being the most common secondary infection acquired while in the intensive care unit (ICU). It is a significant global disease burden and especially prevalent in low- and middle-income countries.CAP, HAP VAP in addition to and pneumonia of the

immunocompromised patient that need Intensive Care clinician. According to the institute of medicine, pneumonia caused 36000 death yearly (DePalo et al. 2010). HAP and VAP estimated about 45% of nosocomial infection (Aarts et al. 2007). An assessment of a patient's pneumonia type is essential for effective therapy(Morris 2018).VAP is developed after 48 hours the patient has intubated while HAP only acquired due to immunocompromised i.e., it is not associated with a device(Agyeman et al. 2020). Treatment with empiric AB starts immediately. However, AB selection related to the type of pneumonia and another factor.(Ibn Saied et al. 2020) Irrational Use of Antibiotics:

2.4. Irrational use of antibiotic

2.4.1. Rational Use of Antibiotics Definition

The German Society of Internal Medicine (DGIM) and other society raise appoint to the term “Choosing Wisely.” The goal is to improve patient treatment further. Significant areas of overuse and ineffective care may be established to consider the diagnosis, treatment, prevention, and exclusion of infectious diseases. Such topics are essential in many medical areas and play a role in the discipline of infectious diseases and the inappropriate use of AB (Jung et al. 2016).

World Health Organization (WHO) defines the rational use of drugs, that the patient receives appropriate medications according to his diagnosis disease, with the right 5’D – Drug, Dose, Delivery, De-escalation, Duration- and at the lowest cost. The 5 D is a practical guide developed to avoid the irrational use of medicine (Jung et al. 2016) (Le Grand, Hogerzeil, and Haaijer-Ruskamp 1999).

Drug use evaluation: It is a system of ongoing criteria-based evaluation of drug use that will help to ensure appropriate use at the individual patient level. This method involves the detailed analysis of individual patient data(Sherman 1994).It is consist of many steps staring from establishing the responsibility, establish the framework and goals Grow, set out criteria for medical evaluation, collecting data and analyzed, make a plan of action and finally follow up (Sherman, 1994).

WHO recommend four intervention established to regulate the drug rational used that target both the prescriber and patient Those intervention applied after DUE result in order to maximize the benefits and minimize the risk of all drug related problem.(Faley and Fanikos, 2017).

2.4.1.1. Process for Rational Prescribing

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

1- Do antibiotic is indicated:

Some disease caused by bacteria and other by viruses. Antibiotic prescribed and effective only for bacterial infection. Also, immune system can define against non-serious infection. Antiseptic could be used for superficial infection (Kollef et al. 2017)(Nauclér et al. 2020)

2- Is this the appropriate antibiotic:

Appropriate antibiotic should be selected to treat the patient according to national and international guidelines, also its usage as a prophylactic or indicated(Tiri et al. 2020). The following factors affect its selection:

i) Suspected pathogen: the suspected pathogen should correlate to the sight of infection, using antibiotic before and the local antibiogram. The culture should be done as soon as possible before administer the empiric therapy in order to determine the susceptibility of the antibiotic

ii) Antibiotic: keep in consideration the spectrum of antibiotic, bioavailability, mechanism of action and patient tolerance

iii) The patient: Many factors related to patient impact antibiotic selection:

- The severity of illness as well as the presence of co-morbidity. Keep in consideration the immunosuppressive, the renal and hepatic function and hemodynamic situation of the patient

- Age: some antibiotic is not prescribed for pediatric and weight is the main factor to be consider, other is given with precaution geriatric according to their renal function, allergy.
- Allergy: penicillin cause allergy to some patient as well as some cross allergy of cephalosporin
- Recent antibiotic use: patient who receive AB during the previous 90 days will help prescriber to indicate the microorganism as the type of antibiotic to be prescribed.
- Pregnancy and lactation: teratogenic AM should be avoided in pregnancy. specific considerations should be taken into account, which is related to both the pregnant woman and her baby.

3- The indication of the treatment:

- Prophylactic treatment: given to prevent an infection that has not yet developed Limited to patient at high risk of developing infection. e.g.: immunosuppressive therapy as cyclosporine after liver transplant, cefazolin before surgery to prevent staphylococcus skin infection of surgical site, cancer patient. Keep in mind risk vs. benefit and duration should be controlled to prevent resistance (Shahzad and Wahid 2014)(Kollef et al. 2017)(Tiri et al. 2020).
- Definitive*:* After culture and sensitivity results are known the definitive treatment can begin. Choose the antimicrobial that is safe, effective, narrow spectrum and cost effective so you avoid toxicity, treatment failure and antimicrobial resistance (Timsit et al. 2019)(Alshareef et al. 2020).
- *Empiric Therapy*: Given to patient who have proven or suspected infection, but the responsible organism(s)has or haven't yet identified (Ali et al. 2019).

4- The route, dose, frequency and duration of selected antibiotic: Patients admitted to the hospital are usually started on IV antibiotic therapy, then switched to equivalent oral therapy after clinical improvement (usually within 72 hours) unless the patient is critically ill and unable to take oral antibiotic, or there is no equivalent oral antibiotic.

Dose and frequency generally should be given as established by guidelines, in some cases should be calculated according to the body weight and renal function.

Duration of antibiotics is important as it is linked to increased emergence of antibiotic resistance, adverse effects and overall cost to the health system. Most bacterial infections in normal hosts are treated with antibiotics for 1–2 weeks. The duration of therapy may need to be extended in patients with impaired immunity e. g., diabetes, alcoholic liver disease, neutropenia, diminished splenic function, etc.., chronic bacterial infections e.g., endocarditis, osteomyelitis, chronic viral and fungal infections, or certain bacterial intracellular pathogens (Lim et al. 2020)(Tiwaskar and Manohar, 2017).

5- *The effectiveness of the treatment:* The best way to reduce overuse of antibiotics is to discontinue antibiotics when no longer required using blood cultures with clinical progress, keeping the antibiotic course as short as possible regarding to the patient's response and symptoms. Biomarkers may be used when deciding on the appropriate duration for antibiotics, but they should be interpreted thoughtfully (Dupuy et al. 2013)(Hellyer et al. 2020).

Antibiotics are misused in both developed and developing countries; sometimes, prescribers write antibiotics for viral or colonization. Another misuse to give the wrong antibiotic or wrong dose or duration.

Patient adherence considers another problem, as some patients did not complete the antibiotic course once the symptoms relieved before the course of the medicine finish (Rajalingam et al. 2016).

2.5. The Most Common Situations in Which the Antibiotics Used Irrationally In ICU

2.5.1. Sometimes AB are prescribed for viral infections or colonization, other situation inappropriate AB section, or without dose optimization ,inappropriate combination or expensive AB(Centers for Disease Control and Prevention 2017)

It is essential to know why providers and consumers behave the way they do to promote the rational use of antibiotics. The utilization of medicines and related products accelerates antibiotic resistance development is a significant part of a recognized global health crisis and danger, sustainability, and growth. Antibiotic Resistance (ABR) is the underlying cause the total volume of antibiotics is, without a doubt require irrational antibiotic usage, in general, that is affected by multiple underlying factors significant contributor(Ali et al. 2019).(Machowska and Lundborg 2019) .

- 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 (Le Grand, Hogerzeil, and Haaijer-Ruskamp 1999).

2.5.2. There are two situations where antibiotics are usually prescribed irrationally; fever and diarrhea

Fever: A high temperature results from many diseases; it is not associated only with infection. Antibiotic products in cases of fever due to non-bacterial cause there are no beneficial effects.

The most popular contagious causes of fever are viral infections and antibacterial antibiotics take little role in their treatment(O'Grady et al. 2008). They do not shorten the duration of the disease or ban secondary infections. The indistinctive use of antibiotics in all cases of fever increases the cost of therapy, harmful effects and drug resistance development and can mask the symptoms of bacterial infection and make it difficult to diagnose properly(Guo et al. 2019).

Antipyretics such as paracetamol can be used with high fever and that antimicrobials are NOT antipyretics should never be forgotten.(Haddad et al. 2018)

Diarrhea: The second condition, often over-prescribed antibiotics. Infectious or non-infectious causes can occur. However, the reality remains that in almost every case it is easy to recover and only requires sufficient rehydration. In all cases of doubt, a cyst, ova, and blood test should be performed. In the presence of severe, or bloody diarrhea, fever, and systemic toxicity, sheep culture can be performed. Antimicrobial therapy indications for diarrheal diseases must be high fever patients, blood-borne diarrhea, severe dehydration and systemic toxicity, ages extremes, histories of recent antibiotic use, recent trips and food poisoning outbreaks in the community (Shane et al. 2017).

Several cases specifically illustrate the usage of antibiotics inadequate, the following example of inadequate uses:

Long-term empirical therapy without clear evidence of infection: Antibiotics are considered to be one of the most common errors when a patient appears not to be responding treatment (Tiwaskar and Manohar, 2017).

Giving antibiotics to positive culture patient without symptoms: The correct therapeutic principle in these situations involves only collecting crops at infection places and avoiding treating positive cultures when signs and symptoms of active infections are missing, such as the colonization of the urinary tract in elderly women (Zilahi et al. 2016).

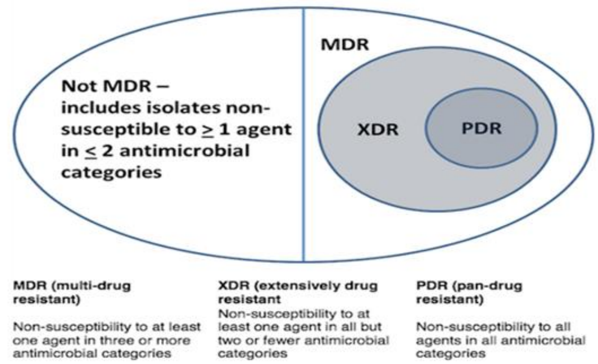
Identification of causative organism but failure to narrow antimicrobial therapy frequently clinicians start with empiric therapy which is based on broad spectrum agents until culture result is determined. When culture and susceptibility data are available, an antibiotic with the narrowest spectrum should be selected for continuation of therapy, but this does not occur, especially, when the patient has good outcomes during taking empiric therapy (Musgrove et al. 2018).

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 (Martin-Loeches, Leone, and Einav 2020).

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 (Pasina, Ottolini and Tettamanti 2019).

The Consequences of Irrational Use of Antibiotics:

- **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 (M. S. Ramirez et al. 2019)". 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. - 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 15 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 (Guanche-Garcell et al. 2011).



- **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).
- **Limited efficacy**: when under-therapeutic dosage of antibiotics is given to the patients (Zhou et al. 2016).
- **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(Souza, Noblat, and Noblat 2008)

2.6. Strategies to Improve Rational Use

A good understanding of the prevalence of such resistance and the factors leading to its creation and dissemination is needed in implementing successful AMR policies and strategies. A good understanding of the prevalence of such resistance and the factors leading to its creation and dissemination is needed in implementing successful AMR policies and strategies (Abram et al. 2020).

- Improving living standards, e.g. vaccination, education, hygiene and the spread of infectious diseases (Uchil et al. 2014).
- Using guidelines for antibiotic (Uchil et al. 2014) (C. R. Lee et al. 2013)
- National restriction-sold only with prescription (Uchil et al. 2014)
- Minimizing Durations of Therapy
- The New Prospective Audit and Feedback: Handshake Stewardship

- Rapid Diagnostic Technology Interventions(Cole, Rivard, and Dumkow 2019)(Bull 2008)(Cole, Rivard, and Dumkow 2019)

WHO advocates 12 key interventions to promote more rational use:

1. Establishment of a multidisciplinary national body to coordinate policies on medicine use
2. Use of clinical guidelines
3. Development and use of national essential medicines list
4. Establishment of drug and therapeutics committees in districts and hospitals
5. Inclusion of problem-based pharmacotherapy training in undergraduate curricula
6. Continuing in-service medical education as a licensure requirement
7. Supervision, audit and feedback
8. Use of independent information on medicines
9. Public education about medicines
10. Avoidance of perverse financial incentives
11. Use of appropriate and enforced regulation
12. Sufficient government expenditure to ensure availability of medicines and staff(Who 2012a)

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

Action Step 1: Vaccinate

- Get influenza vaccine
- Give influenza / S. pneumonia vaccine to at-risk patients before discharge

Action Step 2: Get the catheters out

- use catheters only when essential
- remove catheters when no longer essential

Action Step 3: Target the pathogen

- culture the patient
- target empiric therapy to likely pathogens
- target definitive therapy to known pathogens

Action Step 4: Access the experts

- consult infectious diseases experts for patients with serious infections

Action Step 5: Practice antimicrobial control

- engage in local antimicrobial control efforts

Action Step 6: Use local data

- know your antibiogram

Action Step 7: Treat infection, not contamination

Action Step 8: Treat infection, not colonization

Action Step 9: Know when to say "no" to vancomycin)

Action Step 10: Stop antimicrobial treatment

- when infection is treated or unlikely

Action Step 11: Isolate the pathogen

- use standard infection control precautions
- contain infectious body fluids (airborne/droplet/contact precautions)
- when in doubt, consult infection control experts

Action Step 12: Break the chain of contagion

- stay home when you are sick
- keep your hands clean
- set an example!(Cosgrove et al. 2007).

2.6.1. Characteristic of Inappropriate Use of Antibiotics

Irrational Antibiotics Use Causes

The Most Common Indication Antibiotics Are Used for Irrationa

The Most Prevalent Misuse of Antibiotics:

2.6.2. Strategies Targeted Prescriber Includes Role of Bio Markers

Strategies to Reduce Inappropriate Use of Antibiotic

They can be used to predict how a patient will respond to a medicine or whether they have, or are likely to develop, a specific disease.” (Hellyer et al. 2020).

Biomarkers can thus be used for both prognostic purposes (how a patient will respond) and diagnostic purposes (whether a patient has a specific disease). (Foushee, Hope, and Grace 2012) (European Medicines Agency, 2017).

Biochemical biomarkers are proteins in nature that increase or decrease in case of inflammation or infection. Procalcitonin (PCT), and C-reactive protein (CRP) plays an essential role in infection rapid diagnosis- as they confirm that the host responds to the microorganism (Denny et al. 2020)(Nauclér et al. 2020) PCT consider more accurate for infection diagnosis as it is only increased in this case, as CRP increase in inflammatory cases like myocardial infraction and arthritis (Nargis, Ahamed, and Ibrahim 2014). In Italy, they compare the efficacy of CRP and PCT in ICU to evaluate their role, and PCT shows high efficiency in predicting bacteremia (Bassetti et al. 2018). Another study shows the efficacy to stop antibiotic by measure PCT level as it is decreased when a patient receives the correct antibiotic (Hellyer et al. 2020).

C-reactive protein (CRP)C-reactive protein (CRP) is widely used as a biomarker for bacterial infection, inflammation, and organ failure. it is not infection specific biomarker and undependable to initiate AB or stop it alone, other criteria should be considered(Dupuy et al. 2013) CRP level > 200 make complex with lipoproteins and indicate sever sepsis and poor organs outcome, never the less it is mechanism is not understood (Cheng et al. 2020).CRP used in combination with other criteria of inflammation to initiate, evaluate the response and stop antibiotic(Jankovic et al. 2020).

Procalcitonin : PCT level associate with a serious bacterial infection, initiate AB , response to AB and time out the AB (Kollef et al. 2017). Studies shows the correlation between PCT and other diagnostic criteria like *CURB-65* for pneumonia and *q SOFA* lead to better outcome, decrease in LOS in ICU (van der Does et al. 2018) PCT has a role is to initiate antibiotic as it considers as a diagnostic biomarker also for bacterial infection in ICU but it cannot determine the right empiric therapy; culture should be obtained after PCT elevation, but before empiric therapy initiation(Bassetti et al. 2018) PCT level lead also to evaluate the importance of AB use ; as it decrease in this case. (van der Does et al. 2018) AB time out is correlated to PCT level ; so PCT indicate the recovery and prevent develop of MDR (Kollef et al. 2017),(van der Does et al. 2018).

WHO recommend four intervention established to regulate the drug rational used that target both the prescriber and patient Those intervention applied after DUE result in order to maximize the benefits and minimize the risk of all drug related problem(Faley and Fanikos 2017).

***Interventions targeted at prescribers*:**

Educational materials: Standard treatment guidelines (STGs) consider the main resource to educate the health care provider continuously, approaches to introduce educational materials are flow chart, newsletters, and bulletins. also, printable leaflet considers as a source(Le Grand, Hogerzeil, and Haaijer-Ruskamp 1999). Seminars, workshop, and discussion consider a good approach for education the prescriber and update his information. Applying a of a module on rational drug use in basic and post-basic medical education shows a high impact of importance the rational use of drug.

Managerial strategies Essential drug list, Kit system distribution, Pre-printed order forms, Stock control, Course-of-therapy packaging, Effective package labelling are strategies done to apply the rational use of drug

Financial interventions Buying drugs and paying for it is undesirable for patient, sometimes lead the patient to buy incomplete drugs amount or type because of the cost. So, consider the patient financial state while prescribing medication

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 could result in the black marketing of banned drugs, and may lead to use of (other) irrational drugs

Interventions targeted at patients:

Educational interventions A combination of different educational strategies and materials may be more effective with patients. Patient education is deference from public education. Face to face communication and writing consultation were found to cause considerable improvement in patient compliance to the treatment. General public education can include posters, booklets, mass media, education in primary schools and innovative methods such as theatre, role plays, comics and videos.

Financial interventions some financial interventions such as the establishment of community revolving drug funds was found to ensure regular availability of essential drugs at the community level, then people did not have to rely on the informal market where non-essential drugs are usually provided. However, management of funds and accountability were some of the problems commonly encountered. No evaluations were available on the impact of community revolving funds on community drug use.

Regulatory strategies Although regulatory strategies are not targeted at consumers, their success may depend on the extent to which consumer behavior and demand is addressed

Appropriate indication. The decision to prescribe drug(s) is entirely based on medical rationale and the drug therapy is an effective and safe treatment.

All this intervention and strategies lead to (Le Grand, Hogerzeil, and Haaijer-Ruskamp 1999).

a. Appropriate drug. The selection of drugs is based on efficacy, safety, suitability, and cost considerations.

b. Appropriate patient. No contraindications exist, the likelihood of adverse reactions is minimal, and the drug is acceptable to the patient.

c. Appropriate patient information. Patients are provided with relevant, accurate, important and clear information regarding their conditions and the medication(s) that are prescribed

d. Appropriate evaluation. The anticipated and unexpected effects of medications are appropriately monitored and interpreted.(Sherman 1994)(Fanikos et al. 2014).

2.7. Antibiotic Stewardship Program

The effort to measure and enhance how antibiotics are prescribed and used by clinicians is antibiotic management. Improving the prescribing and usage of antibiotics is crucial in successfully curing diseases, shielding patients from excessive antibiotic damage and combating antibiotic resistance (Page last reviewed: August 15, 2019 Content source: (CDC, 2014).

2.7.1. Provider-based Interventions

Antibiotic “timeouts”: In hospitalized patients, antibiotics are typically initiated empirically. Providers frequently do not review antibiotic selection after additional data (including cultures) is available. An antibiotic pause is an on-going re-assay of the need for and option of antibiotics until the clinical image becomes better and more medical evidence becomes available, in specific crop tests and fast diagnoses. 9 Timeouts for antibiotics vary from the potential evaluation and reviews, as suppliers are checking, not the stewardship team. A trial showed that 48-72-hour therapy antibiotic timeouts improved selection appropriateness, but did not decrease overall antibiotic use (Thom et al. 2018).Timetables against antibiotics constitute a useful additional procedure, but the stewardship program is not a substitute of future audits and feedback. The optimal timing has not been identified of antibiotic timeouts. Experts say that regular antibiotic collection reviews will improve therapy before a definite diagnosis and care period is identified. Antibiotic studies performed by hospitals will concentrate on four main issues(Tamma, Miller, and Cosgrove 2019) :

- Does this patient have an infection that will respond to antibiotics?
- Have proper cultures and diagnostic tests been performed?
- Can antibiotics be stopped or improved by narrowing the spectrum (also referred to as "**de-escalation**") or changing from intravenous to oral?
- How long should the patient receive the antibiotic(s), considering both the hospital stay and any post-discharge therapy?

Assessing penicillin allergy: Approximately 15% of patients in hospital record penicillin allergy(C. E. Lee et al. 2000) . Nevertheless, a serious penicillin reaction prohibiting diagnosis with a beta-lactam antibiotic is present in fewer than 1% of the US population (Cherazard et al. 2017). Many reliable forms are possible to better determine reactions to penicillin, including background and clinical evaluation, challenge doses and skin monitoring (Centers for Disease Control National Center for Emerging and Zoonotic Infectious Diseases 2016).

Pharmacy-based Interventions

Pharmacists also implement and/or integrate the following procedures electronic patient reports prescription sections:

Documentation of indications for antibiotics: The requirement for an indicator of the dosage of antibiotics can encourage certain procedures, such as a potential examination or reviews and improvement of care post-discharge times (Timmons et al. 2018).

• **Automatic changes from intravenous to oral antibiotic therapy**: This adjustment will increase the health of patients by growing the need for intravenous treatment and antibiotics with sufficient absorption in suitable circumstances.

• **Dose adjustments**: When required, in particular renal or therapeutic drug-based monitoring, for example in case of organ dysfunction.

• **Dose optimization**: For example, extended-infusion beta-lactam administration particularly in seriously ill and drug-resistant patients.

• **Duplicative therapy alerts**: Alerts when treatment can be inappropriately duplicative with double agents using overlapping spectra at the same time (e.g. anaerobic activity and resistant Gram-positive activity) (Rattanaumpawan et al. 2011)(Schultz et al. 2014).

Time-sensitive automatic stop orders: In specific, antibiotics provided for surgical prophylaxis in order to determine antibiotic medications.

• **Detection and prevention of antibiotic-related drug-drug interactions**: for example, interactions between some orally administered fluoroquinolones and certain vitamins.

2.7.2. Microbiology-based Interventions

The microbiology lab in consultation with the stewardship program often implement the following interventions:

• **Selective reporting of antimicrobial susceptibility testing results**: tailoring hospital susceptibility reports to show antibiotics that are consistent with hospital treatment guidelines or recommended by the stewardship program(Langford et al. 2016).

• **Comments in microbiology reports**: for example, to help providers know which pathogens might represent colonization or contamination (Musgrove et al. 2018).

Nursing-based interventions

Bedside nurses often initiate the following interventions:

• **Optimizing microbiology cultures**: Knowing proper techniques to reduce contamination and indications for when to obtain cultures, especially urine cultures(Summary 2019) .

• **Intravenous to oral transitions**: Nurses are most aware of when patients are able to tolerate oral medications and can initiate discussions on switching to oral antibiotics.

• **Prompting antibiotic reviews ("timeouts"):** Nurses often know how long a patient has been receiving an antibiotic and when laboratory results become available. They can play a key role in prompting reevaluations of therapy at specified times, such as after 2 days of treatment and/or when culture results are available(Olans, Olans, and DeMaria 2016).

Impact of Pharmaceutical care in rational drug use

2.8. Common Infection-based Interventions

More than half of all antibiotics given to treat active infections in hospitals are prescribed for three infections where there are important opportunities to improve use: lower respiratory tract infection (e.g. community acquired pneumonia), urinary tract infection and skin and soft tissue infection(Magill et al. 2014) . Optimizing the duration of therapy can be especially important because many studies show infections are often treated for longer than guidelines recommend and data demonstrate that each additional day of antibiotics increases the risk of patient harm (Branch-Elliman et al. 2019) .

Examples of interventions are below and summarized

Community-acquired pneumonia:

- Interventions have focused on:
- Improving diagnostic accuracy
- Tailoring of therapy to culture results
- Optimizing the duration of treatment to ensure compliance with guidelines

The use of viral diagnostics and/or procalcitonin might help identify patients in whom antibiotics can be stopped because bacterial pneumonia is unlikely(Branche et al. 2015). Optimizing the duration of therapy at hospital discharge is especially important as most excess antibiotic use in the treatment of community-acquired pneumonia occurs after discharge (Vaughn et al. 2019)(Madaras-Kelly et al. 2016) .

Urinary tract infection (UTI): Many patients who are prescribed antibiotics for UTIs have asymptomatic bacteriuria that generally does not need to be treated. Successful stewardship interventions focus on avoiding obtaining unnecessary urine cultures and avoiding treatment of patients who are asymptomatic, unless there are specific reasons to treat(Trautner et al. 2015) .For patients who need treatment, interventions can focus on ensuring patients receive appropriate therapy based on local susceptibilities for the recommended duration(Slekovec et al. 2012) .

Skin and soft tissue infection: Interventions have focused on ensuring patients with uncomplicated infections do not receive antibiotics with overly broad spectra (e.g. unnecessary coverage for methicillin-resistant Staphylococcus aureus (MRSA) and gram-negative pathogens) and prescribing the correct route, dosage and duration of treatment (Stevens et al. 2014)(Jenkins et al. 2011).

Sepsis: Early administration of effective antibiotics is lifesaving in sepsis. Antibiotic stewardship programs should work with sepsis experts in the hospital, along with the pharmacy and microbiology lab, to optimize the treatment of sepsis. Important issues to address are:

• Developing antibiotic recommendations for sepsis that are based on local microbiology data.

• Ensuring protocols are in place to administer antibiotics quickly in cases of suspected sepsis.

• Ensuring there are mechanisms in place to review antibiotics started for suspected sepsis so that therapy can be tailored or stopped if deemed unnecessary(Al-Sunaidar, Abd Aziz, and Hassan 2020).

Culture proven invasive infection: Invasive infections (for example infections from the blood stream) provide the potential for antibiotic treatment because they are detected quickly and are sometimes driven to worse outcomes by sub-optimal therapy. Future audit and feedback of new cultures or quick diagnostic results can be beneficial in particular if necessary, to reduce the time required to discontinue, narrow or extend antibiotic therapy(Jenkins et al. 2011).

2.9. Previous Studies Investigate Antibiotic Utilization in developing countries

In almost all EU countries the general health impendence is viewed as healthcare-associated infections (HAIs) and antimicrobial resistance. In 2008, the European Center for Disease Prevention and Control (ECDC) proposed the routine and integrated weight of total HAIs in the European Union.

In the course of the 'Hospitals in Europe Link for Infection Control through Surveillance (HELIS),' project, 2000-2003 was taken as the starting steps to standardization for HAI monitoring in Europe. In 2004 and 2005, and later as a part of the network "Enhancing Patient Health in Europe (IPSE)" from 2005 to 2008, the HELIcS performed a systematic surveillance of its HAIs and were passed to ECDC in July 2008.

Study conduct in Norway by Naylor et al, showed a total of 1756 patients. In the guidelines adherent group, the thirty-day mortality and in-hôpital mortality were lower (OR = 0.48, p = 0.003 and OR = 0.46, p Compliance with the guidance has no effect on readmission for 30 days. The LEA was analyzed in lineary regression (mean difference = 0.47, 95 percent CI-1.0,02, (0.07), p = 0.081) when LEA was analyzed for patients released alive. The adhesive community had a sub-distribution danger ratio (SHR) of 1,17-95 % CI (1.02, 1.34), p=0,025 in contrast with the non-adherent category in the market vulnerability evaluate for LOS(Wathne et al. 2019).

A study conducts in Turkey by Ozlem Tunger et al showed that the rate of antibiotic use decreased from 16.6% to 11.3%, rational use increased after the restriction policy (p<0.001) that the Turkish government applied. Besides the specific antibiotic use increasing, prophylactic antibiotic use was found to decrease (p<0.001). Mostly determined irrationality was the prophylactic use in both studies. As expected, infectious disease specialist examinations increased the appropriate antibiotic use(Tunger et al. 2009).

Another one by Nergis Asgin et al Ampicillin, gentamicin, vancomycin, and teicoplanin were confirmed to have resistance to all 47 VRE strains obtained from regeneration (n=35) and blood (n= 7) and urine (n = 5) samples. An E. Linezolid resistant was faecium isolate at an intermediate stage. No quinupristin – dalfopristin or daptomycin resistance was present. The only vanA between strains was detected. PFGE results show 31 out of 47 strains with a clustering rate of 66 % were clonally linked. There has been no common clone(Asgin and Otlu 2020).

In the study by YILDIZ et al , a total of 147 CRE drug-resistant (MDR) or substantially drug-resistant (XDR) strains were used in the colistin broth and Fosfomycin agar dilution method. Klebsiella pneumonia (91.16%), Escherichia coli (7.48%), Enterobacter cloacae

(0.68%) and Serratia marcescens (0.68%) were included in the study. They all produce different kinds of carbapenems, including OXA-48, NDM, and KPC. Some of those strains have three different mechanisms for carbapenemase, OXA-48 (78.23%), NDM (2.04%), KPC (0.68%), OXA-48 and NDM (10.88%), OXA-48 and KPC (0.68%). Roughly 76.19% were resistant to colistin and Fosfomycin and 67.35% were resistant to strains. A maximum of 21 out of 35 strains responsive to colistin has been identified to be Fosfomycin prone. The study found that colistin and Fosfomycin had strong resistance levels. CRE strains MDR and XDR distributed throughout our region and should also be accompanied by a control method for CRE. Besides, in all stationery and outpatient settings, the applicability of antimicrobial management programs must be increased (Yildiz et al. 2019).

3. METHODOLOGY

3.1. Study design

A retrospective record review of antibiotic utilization patterns in the intensive care unit ICU between 1st January 2016 and 31st December 2019. The data obtained from patient files at the archive and electronic system records in Near East University Hospital (NEUH).

3.2. Setting

This study has been conducted in Northern Cyprus,' Near East University Hospital (NEUH).

The medical center is one of the biggest in Cyprus. There is a hospital closing area of 55,000 square meters, 209 single-patient rooms, Intensive Care Unit with 30 beds, eight operational theatres, 14-bed intensive care center with Neonatal intensives.

3.3. Study subjects

All the ICU files of patients admitted within the stipulated study period were analyzed.

- Inclusion criteria
    - Patients ≥18 years
    - Patients who hospitalized between 1st Jan. 2016 and 31st Dec.2019
    - Patients stay more than 24 hours
    - Patients used at least one AB
- Exclusion criteria:
    - Patient with misinformation or incomplete file
    - A Patient who stay less than 24 hours

3.4. Data collection tool

The ICU chart records all the information that is necessary when prescribing antibiotics. Using this as a data collection tool allowed the researchers to collect information on antibiotic use from the ICU charts.

- Patient demographic details: Age, Gender
- Usage of antibiotics: Type of AB, Dose of AB, Route of administration of AB, Combination of AB
- Date of admission and date of discharge: to assess the LOS
- Diagnosis
- ICU devices used
- Culture and microorganism: to evaluate the de-escalation concept

3.5. Guidelines and clinical resources

The rationale of the prescribed antibiotic was analyzed using the Infectious Diseases Society of America (IDSA), guidelines for CDCs, Up-TO- Date, Sanford guidelines, and John Hopkins guidelines. It analyzed step-by-step by a clinical pharmacist the selection of medication, doses, and doses frequency. The rationality of antibiotics has also been studied in the field of antibiotic drugs.

3.6. Statistical analysis

Microsoft Excel 2016, and statistical package for the Social Sciences (SPSS), Software Version 26.0, were used to collect and analyze the data. Statistical methods were used to analyze the data, including the calculation of descriptive statistics such as the frequency and percentage for categorical variables, the weighted mean, the median, the standard deviation (SD), and the minimum and maximum for the continuous variables. To evaluate the associations between categorical variables, a Pearson Chi-square test, and Binary Logistic Regression were performed. The level of significance was defined as $\alpha=0.05$.

4. RESULTS

There were 522 patients admitted to ICU between 1st, Jan. 2016 and 31st, Dec. 2019, 352 patients included in the analysis. Patients admitted less than 24 hours, did not use an antibiotic, younger than 18 years old, and the incomplete file was excluded from the study.

Table 1. Characteristcs of Patients

	Frequency	Percentage
Gender		
FEMALE	168	47.70%
MALE	184	52.30%
Age		
Not Ger	105	29.90%
Geriatric	246	70.10%
Ventilator		
NO VENTLATOR	144	40.90%
VENTILATOR	208	59.10%
IRR2		
Irrational	244	69.50%
Rational	107	30.50%
Diagnosis		
Respiratory	165	47.00%
Internal	8	2.30%
Surgery	5	1.40%
Oncology	13	3.70%
Anesthesia	160	45.60%
Status		
Death	214	61.10%
Alive	137	39.00%

There were 168(47.7%) females and 184(52.3%) males with average age 70.88 years, SD (±16.297), 208 (59.1%0) patients were ventilated, and 144 (40.9%) were did not use the ventilator. The none geriatric population was 105 (29.9%), and the geriatric population was 246(70.1%). The total mortality rate was out of 228 (64.6%). There were 244(69.5%) patients who receive irrational antibiotics, while 107(30.5%) patients receive rational medicine.

Table 2: Department

Department	Frequency	Percent
NUOROLOGY	7	2.0%
ONCOLOGY	13	3.7%
INTERNAL	14	4.0%
RESPIRATORY	163	46.2%
CARDIOLOGY	26	7.4%
GENERAL SURGERY	19	5.4%
ANTHESIA	110	31.3%
Total	352	100.0%

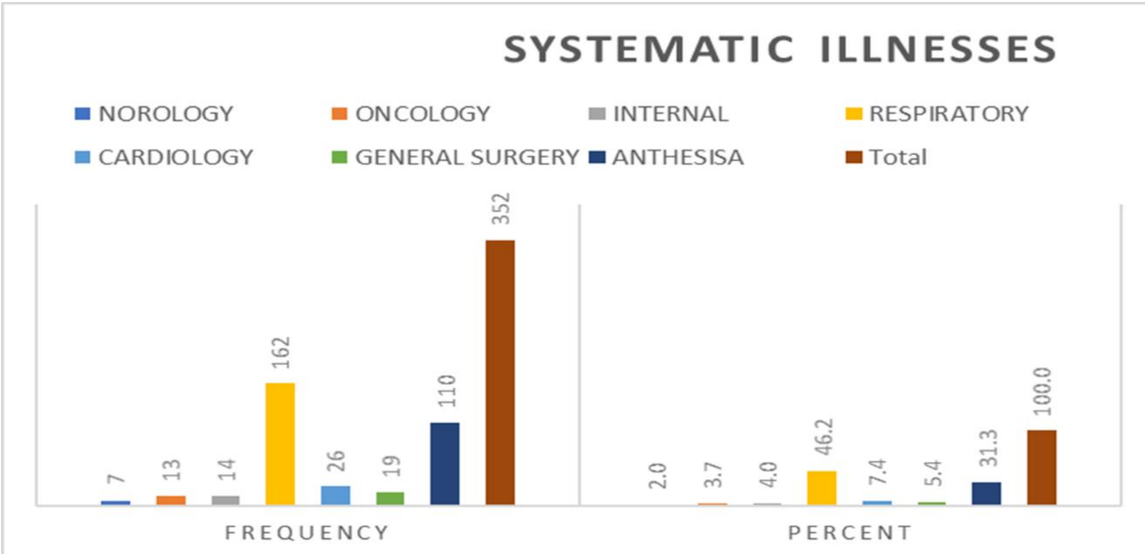


Figure 1: Systematic Illnesses

Out of 352, there were 162(46.2%) patients admitted due to respiratory disorder follow by110 (31.3%) anesthesia, while the lowest cause of admission was neurology disease.

Table 3: Type of diseases

Diseases	Frequency	ICD code
PNOMONIA	145	57.5%
COPD	21	8.%
CANCER	21	8.3%
GDB	28	11.11%
SEPTIC SHOCK	8	3.2%
COMA	27	10.7%
SEPSIS	32	12.7%
SEIZURE	5	1.98%
CARDIAC DISEASE	27	10.7%
BARAIN SURGERY	13	5.2%
MUTIFRACTURE	9	3.19%
INTARABDOMINAL BLEEDING	3	1.19%
FEVER	5	1.98%
others	9	3.57%
Total	**252**	**100%**

This table show that the most common disease for admission is Pneumonia.

Table 4: Distribution of Antibiotics by Groups

	Frequency	Percentage
Aminoglycosides		
Amikacin	5	1.40%
Gentamicin	11	3.10%
Cephalosporins		
Ceftriaxone	85	24.20%
Ceftazidime	12	3.40%
Cefuroxime	28	8.00%
Cefazolin	24	6.80%
Carbapenems		
Meropenem	144	41.00%
Ertapenem	9	2.60%
Imp-Cilas.	10	2.80%
Glycylcycline		
Tigecycline	21	6.00%
Fluroquinolones		
Levofloxacin	29	8.30%
Ciprofloxacin	98	27.90%
Moxifloxacin	25	7.10%
Glyco-lipopeptides		
Vancomycin	28	8.00%
Daptomycin	1	0.30%
Teicoplanin	59	16.80%
Penicillin		
Amoxiclavs	1	0.30%
Pip-Tazo	139	39.60%
Amp-Sulb	25	7.10%
Oxazolidinones		
Linezolid	46	13.10%
Macrolides		
Clarithromycin	17	4.80%
Nitroimidazoles		
Metronidazole	26	7.40%
Antifolate		
TMP-SMX	11	3.10%
Polymyxin		
Colistin	38	10.80%

Table 5: Culture

Culture	Frequency	Percent
NEGATIVE CULTURE	99	28.9%
POSITIVE CULTURE	253	71.8%
Total	352	100.0

The previous table showed that the patient with positive culture is 71.8% while the negative are 28.9%

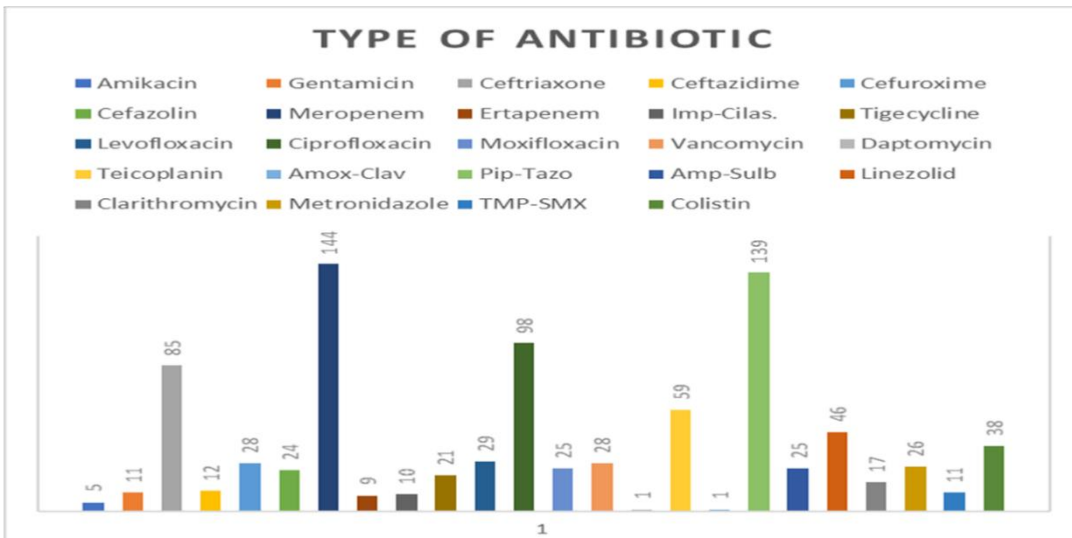


Figure 2: Distribution of Antibiotics by Groups

Data show the most used antibiotic is Meropenem 144(41%) followed by Piperacillin-tazobactam 139(39.6%) then Ciprofloxacin 98(27.90%).

Table 6: DDD & DOT/ admission in 4 years

	2019	/admission	2018	/admission	2017	/admission	2016	/admission
DDD of Amikacin	31	0.16	30	0.28	0	0	0	0
DDD of TMP-SMX								
DOT of Ceftriaxone	315	1.64	174	1.67	92	1.53	20	0.95
DDD of Ceftriaxone	344	1.79	206	1.98	90	1.5	27	1.28
DOT of Pip-Tazo	521	2.71	251	2.41	363	6.05	40	1.90
DDD of Pip-Tazo				0		0		0
DOT of Teicoplanin	395	1.64	88	0.84	188	3.13	0	0
DDD of Teicoplanin	93460	486.77	24640	236.92	58560	976	0	0
DOT of Clarithromycin	63	0.32	23	0.22	7	0.11	6	0.28
DDD of Clarithromycin	63000	328.12	17500	168.26	3500	58.33	6000	285.71
DOT of Levofloxacin	129	0.67	43	0.413	38	0.63	5	0.23
DDD of Levofloxacin	32250	167.96	11250	108.17	9500	158.33	1250	59.52
DOT of Ceftazidime	81	0.42	77	0.74	6	0.1	0	0
DDD of Ceftazidime	692	3.60	976	9.38	48	0.8	0	0
DOT of Meropenem	654	3.40	343	3.29	395	6.58	61	2.90
DDD of Meropenem	4588.5	23.89	2418.5	23.25	3076.5	51.27	318	15.14
DOT of Metronidazole	137	0.713	16	0.15	18	0.3	25	1.19
DDD of Metronidazole	111000	578.12	24750	237.98	14550	242.5	29250	1392.85
DOT of Amox-Clav	5	0.026	0	0	0	0	0	0
DDD of Amox-Clav	54	0.28	0	0	0	0	0	0
DOT of cef-sulb	170	0.88	59	0.56	7	0.11	0	0
DDD of cef-sulb	2697	14.04	876	8.42	126	2.1	0	0
DOT Tigecycli	152	0.79	47	0.45	25	0.41	0	0
DDD Tigecycli	1500	7.81	345	3.32	175	2.91	0	0
DOT of Daptomycin	16	0.08	0	0	0	0	0	0
DDD OF Daptomycin	2240	11.66	0	0	0	0	0	0
DOT of Linezolid	210	1.09	146	1.40	108	1.8	14	0.66
DDD of Linezolid	394200	2053.12	272601.5	2621.168	218880	3648	26880	1280
DOT17 Colistin	296	1.54	94	0.903846	91	1.51	0	0
DDD17 Colistin				0		0		0

DOT of Ciprofloxacin	281	1.46	0	0	311	5.18	43	2.047
DDD of Ciprofloxacin	104200	542.70	88100	847.11	133400	2223.33	15600	742.85
DOT of Moxifloxacin	118	0.61	47	0.451	39	0.65	0	0
DDD of Moxifloxacin	16800	87.5	7520	72.31	6480	108	0	0
DOT Amp-Sulb	75	0.39	21	0.20	28	0.46	23	1.09
DDD Amp-Sulb	204	1.06	55.5	0.53	109	1.81	23	1.09
DOT Vancomycin	190	0.98	43	0.41	98	1.63	12	0.57
DDD Vancomycin	609	3.17	98	0.94	416	6.93	12	0.57
DOT Gentamicin	6	0.03	33	0.32	7	0.11	9	0.42
DDD Gentamicin	192	1	864	8.31	326.4	5.44	345.6	16.45
DOT Cefuroxime				0		0		0
DDD Cefuroxime	0	0	0	0	0	0	324000	15428.57
DOT Ertapenem				0		0		0
DDD Ertapenem	0	0	339000	3259.61	0	0	0	0
DOT of Imp-Cilas.	10	0.052	86	0.82	2	0.033333	0	0
DDD of Imp-Cilas.	0	0	0	0	4000	66.66667	0	0

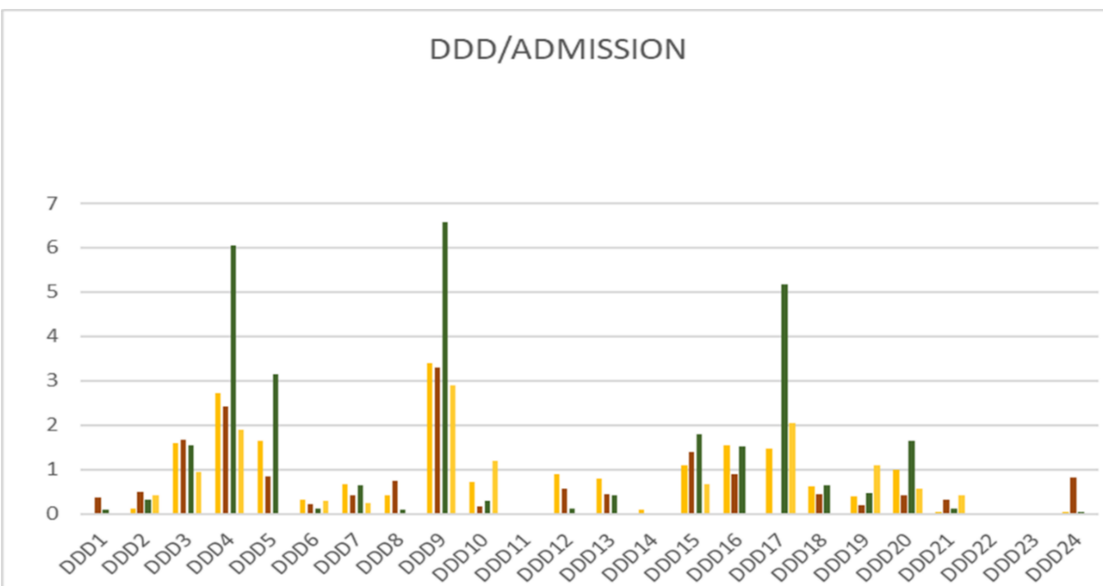


Figure 3: DDD admission in 4 years

The most antibiotic used in 2016 was Cefuroxime, in 2017 was Linezolid, 2018 was Ertapenem and 2019 was Meropenem. Ceftriaxone and Meropenem consumption during 2018 and 2019 almost similar, Teicoplanin is increased significantly in 2019. Ampicillin sulbactam, ciprofloxacin and vancomycin were mostly consumption 2017. in 2018 ceftazidime and lionized were the most frequent used

Table 7: Rationality of Drug

	Frequency	***Percent***
Irrational	245	69.6%
Rational	107	30.4%
Total	352	100.0%

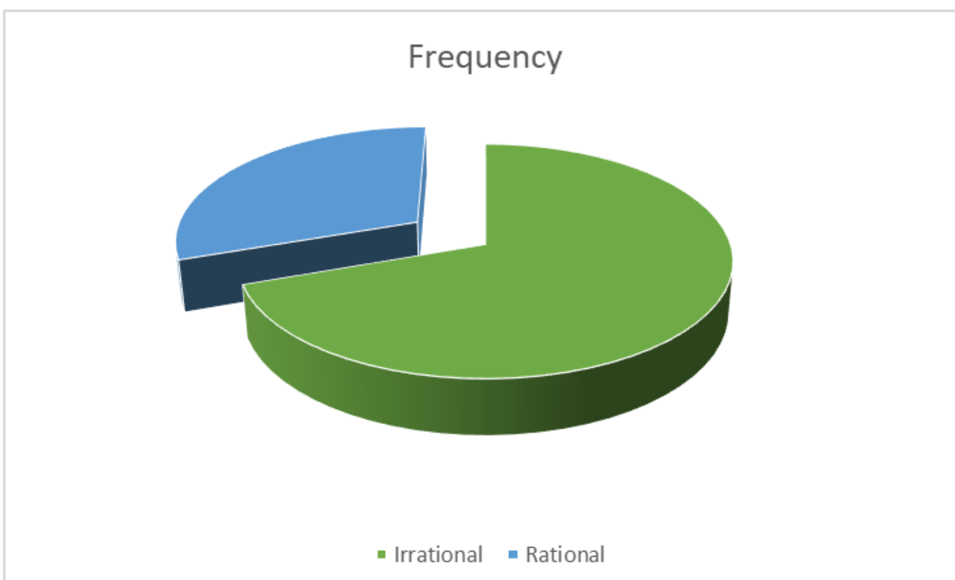


Figure 4: Rationality of Drug

Only 30.4% received rational antibiotics, but 69.6% had at least one problem with the antibiotic they received.

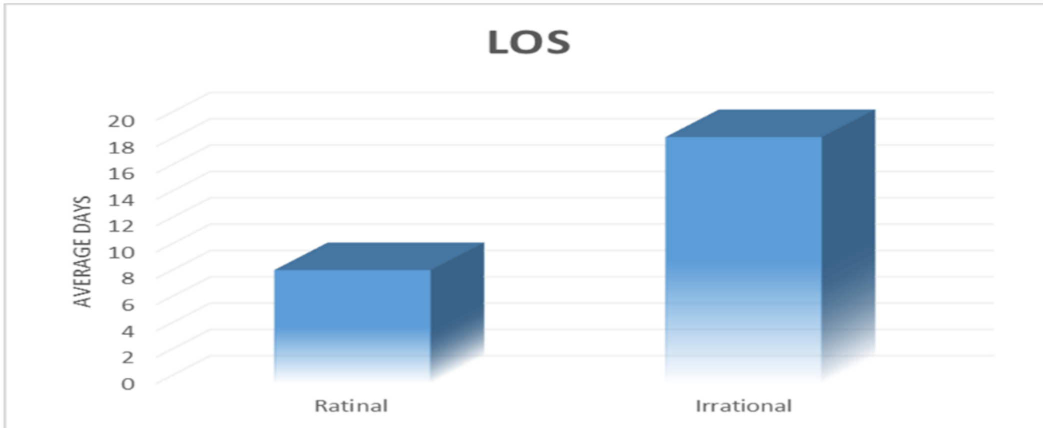


Figure 5: length of stay for patients

The data showed that the staying period for rational drug used patient was significantly lower than irrational. (8.6±9.0) (18.7±25.5) days ($p<0.005$) respectively.

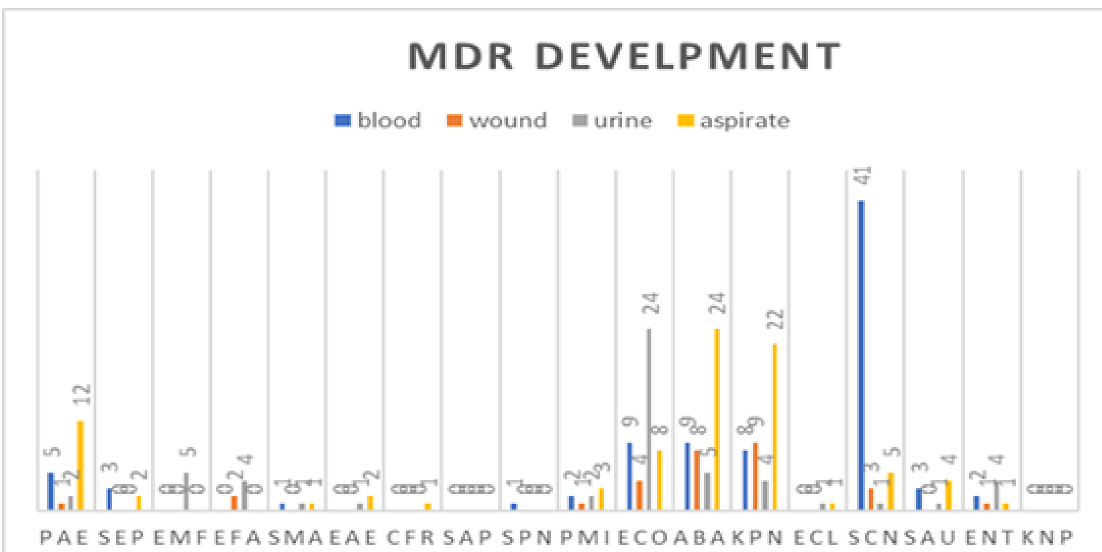


Figure 6: Type of MDR that developed

The 2019 antibiogram shows that the most prevalence MDR in blood is Staph coag-neg (R) (48.8%) followed by A. baumanii, E. coli(10.7%), Klebs ESBL(9.5%). in urine E. coli(43.6%), and in Aspirate by A. baumanii(27.9%) and Klebs ESBL(25.5%)

According to Pharmaceutical Care Network Europe PCNE the main type of drug related problems in Antibiotics used was found that the highest frequency problem is due to dose section , then treatment duration and least is drug section.

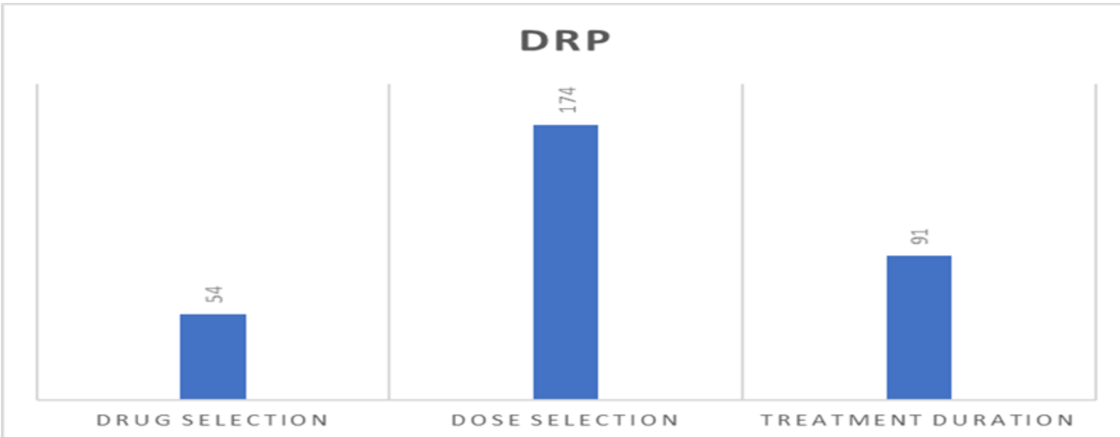


Figure 7: Drug Related Problem

Figure 5 shows the drug related problem according to PCNE , Long duration of treatment was the major problem (28.9%) of Patients who received antibiotic and their microbial culture are negative .

Table 8: Drug Related Problem

DRP	frequency	percentage
Inappropriate drug according to guidelines/formulary	4	1.4%
Inappropriate drug	2	0.7%
No indication for drug	1	0.35%
Inappropriate combination of drugs, or drugs and herbal medications, or drugs and dietary supplements	10	3.5%
No or incomplete drug treatment in spite of existing indication	28	9.89%
Too many drugs prescribed for indication	9	3.2%
Drug dose too low	68	24.1%
Drug dose too high	20	7.06%
Dosage regimen not frequent enough	24	8.5%
Dosage regimen too frequent	26	0.092
Duration of treatment too short	5	0.018
Duration of treatment too long	86	0.304
	283	

And according to CDC Assessment for combinations of antibiotics that are likely to be unnecessary, data show the following result.

Table 9: Unnecessary Combination

Unnecessary Combination		
Irrational colistin combination	11	20.30%
Concurrent use of multiple beta-lactams and/or carbapenems	17	31.40%
Concurrent use of multiple agents with anti-anaerobic activity	23	44.20%
Concurrent use of a respiratory fluoroquinolone with a macrolide.	3	5.70%
total	54	100%

Table 10: Regression Test of Mortality

Variables in the Equation

		B	S.E.	Wald	df	Sig.	OR	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	IRR2(1)	-.215	.251	.734	1	.392	.807	.493	1.319
	MDR2(1)	.566	.263	4.654	1	.031	1.762	1.053	2.948
	AGE2(1)	.282	.250	1.274	1	.259	1.326	.812	2.164
	Staying2(1)	.370	.265	1.960	1	.162	1.448	.862	2.432
	PCT5			6.543	2	.038			
	PCT5(1)	-.586	.276	4.489	1	.034	.557	.324	.957
	PCT5(2)	-.678	.291	5.437	1	.020	.508	.287	.898
	Gender	-.173	.233	.554	1	.457	.841	.533	1.327
	Diagnosis2	-.079	.060	1.719	1	.190	.924	.821	1.040
	Constant	-.288	.437	.433	1	.511	.750		

a. Variable(s) entered on step 1: IRR2, MDR2, AGE2, Staying2, PCT5, Gender, Diagnosis2.

In this regression test of mortality showed the association with MDR development ($p<0.05$) and also with increase in PCT ($p<0.05$). Other factor has no significance association.

Table 11: Relation Between Mortality and Irrationality

Chi-Square Tests

	Value	df	Asymptotic Significance (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	2.281[a]	1	.131		
Continuity Correction[b]	1.936	1	.164		
Likelihood Ratio	2.262	1	.133		
Fisher's Exact Test				.154	.082
Linear-by-Linear Association	2.275	1	.131		
N of Valid Cases	352				

a. 0 cells (0.0%) have expected count less than 5. The minimum expected count is 41.64.

b. Computed only for a 2x2 table

Pearson Chi square test shows that mortality is significant not associated with irrationality

5. DISCUSSION

This study finds that the irrational use of antibiotics is associated with the development of MDR, an increase of (LOS), and morbidity. Increasing the appropriateness in using antibiotics can be achieved by identifying common problems and irrational drug use causes. All countries must recognize these issues and order using quantitative and qualitative techniques to perform surveillance research for monitoring antibiotic usage as the irrational use contributes to the problems mentioned above (Lim et al. 2020b) (He et al. 2019).

AMR is contributed to irrational use directly, and it is a global concern (Kollef et al. 2017). About 60% of AB is used irrationally in a hospitalized patient.

Out of 352 patients, there was only 30.4% received rational antibiotics, but 69.6% had at least one problem in Antibiotic they received. A study done by Kadir in Turkey shows that there is a high resistance of AB and increase in mortality due to irrational use(Tuncay et al. 2020), another one in Saudi Arabian showed the irrational use of AB in their negative outcome on population (Alhomoud et al. 2017), also in Iran got the same result (Mohebbi et al. 2018). The most common problem was using antibiotic without indication, or no national or international guidelines followed, using Antibiotic for viral infection or in case of fever related to another issue, and not stop antibiotic even if the culture-negative

Two previous studies were done in our hospital regarding the antibiotic pattern utilization in two different wards, (The first one had been done in all departments and the second in pediatric) both of them show the irrational antibiotic use-related problems and increase the cost. This is the first one done in ICU (Jame et al. 2019).

Physician are under pressure to prescribe antibiotic in the ICU even though they are not required, however antibiotic given in short time after admission, there must stop once they confirmed to unnecessary (Zilahi et al. 2016) Broad spectrum antibiotic or inappropriate antibiotic also should be de-escalate to narrower spectrum once the culture result is known (Timsit et al. 2019)(De Bus et al. 2016) .In this study data shows that the de-escalation or time-out of antibiotic concept is not applied routinely.

Most of the time the physician obliged to write antibiotic for the critical ill patient to avoid other complication, however keep in consideration many criteria related to the patient himself, local microorganism widespread, and local resistance. Nevertheless, sometimes this antibiotic may be inappropriate or even un-needed(Guven and Uzun 2003).

The ICU is known for its high antibiotic utilization. In this study, 67.7% during 2016-2019 of patients admitted in the ICU received antibiotics for at least one day , similar result obtained in Pakistan(Ailing, Huifang, and Qin 2018) .in Belgium a study shows lower percentage than our study 51.6% of the patients who is admitted to ICU receive AB (Claus et al. 2013), However, higher values ranging from 80% - 95% were seen in the studies (Akl et al. 2014)(Patanaik et al. 2015). This means that ICU is sometimes used antibiotics frequently

Lower utilization as reported by previous study contribute to consideration of CCl in each patient (Claus et al. 2013).

The disparity may be due to the diverse population, the size and specialty of hospitals being studied where the studies have been conducted. The pattern of antibiotic prescription differs from hospital to hospital from one ward to another and from one hospital.

Meropenem and Piperacillin/tazobactam which are B-lactam antibiotics were the most common antibiotics prescribed in the NEUH ICU. While in other studies reported that piperacillin-tazobactam and amoxicillin/clavulanic acid were amongst the five most prescribed antibiotics in the ICU (Anand et al. 2016). Likewise, penicillin antibiotics (cephalosporine) was the most used antibiotics in a study by E. Tacconelli(Tacconelli et al. 2020) in Italy. The antibiotic usage trend in NEUH could be attributed to penicillin antibiotics being one of the first line antibiotics on the hospital formulary.

In this study, lesser utilization of Amoxiclavs, Daptomycin, Amikacin, Ertapenem and Imp-Cilas. was documented, and this was against to results found by(Aubin et al. 2017)(Galar et al. 2019)(Carrié et al. 2020). Restrictive protocols have been used to reduce antibiotic consumption (Huang et al. 2018). Unfortunately, in our study there is no restricted antibiotics were used.

Furthermore, the antibiotics utilization shown in this analysis differed significantly from 1 day to 6 month, with an average of 18 days comparing with other study that found 1-49 days hospitalized in ICU (Molayi et al. 2018). Another one shows the B-lactams is the most used antibiotic in ICU(Axente et al. 2017).

Missed doses were not infrequently noted in this study. Missing of antibiotic doses could lead to sub therapeutic levels increasing the emergence of resistant pathogens (Patel et al. 2019).

About 62.2 % of the patients used combination antibiotic especially between carbapenem and fluoroquinolone., as the major diagnosis on NEUH hospital is Pneumonia and this is one of the recommended therapy by IDSA (Kalil et al. 2018).

Clinicians must strike the right balance between appropriate empiric antibiotics coverage and taking into account the prevention of high-pressure selection(Machowska and Lundborg 2019).

The over-use of empirical antibiotic is related to antibiotic resistance, while the optimum empirical selection is related to reduced mortality in extreme sepsis and septic shock patients.(Uchil et al. 2014)(WHO Regional Office for Europe 2014).

Result from this study showed that the most empiric selected antibiotics in the ICU were Meropenem and piperacillin/tazobactam. Other studies shows that ceftriaxone is the most used AB in ICU in Italy (Tacconelli et al. 2020).

The average LOS reported in this study was 15.68.dayss Comparable with other range of 5 days was seen in the studies by KLK Sneha (Sneha et al. 2019) However, another ranges of 5.75 was seen in study (Aung et al. 2020). in Canada the average days for ICU admission is 4.4 to 4.7 (Evans et al. 2018); it is consider high. Retrospective study in multicenter in Pakistan shows that irrational use of AB contribute to increase LOS and complication(Iftikhar et al. 2019).

The major diagnosis of ICU admission is respiratory disorder with percentage of (46.2%), followed by anesthesia, nevertheless patient start antibiotic immediately without documented the full criteria of the patients, other study showed that follow a diagnosis criteria , evaluate the patient and documented has a significant better outcome for patient (Leekha, Terrell, and Edson 2011).

28.9% of the patient receive antibiotic without stop it in spite there culture was negative and unfortunately 31.5% of total patient develop MDR.

Our antibiogram shows that the most prevalence MDR in blood is Staph coag-neg followed by A. baumanii, E. coli, KlebsESBLin urine E. coli ,and in Aspirate by A. baumanii and KlebsESBLwhich all developed due to irrational use of the antibiotic. Arjen M. Dondorp in his study shows also the use of carbapenem and broad spectrum antibiotic for long time lead to develop MDR(Dondorp, Limmathurotsakul, and Ashley 2018). Bianco et al in his study which done over 4 years to evaluate the irrational use of antibiotic associated with MDR develop (Bianco et al. 2018). Another study done in our hospital byKaya Süer raise a concern about MDR in the hospital (Ruh et al. 2019)(Güvenir, Güler, and Süer 2019). A study done by Cheryl Travasso who found that MDR development with irrational use , on the other hand less use of antibiotic lead to decrease LOS and MDR development (Travasso 2016).

Overall, it is important to understand clearly the sensitivity of the microorganism in order to enable appropriate choice of empiric antibiotics and improve adequate therapy to reduce antibiotic resistance. Knowledge of the present susceptibility patterns also can be used to ascertain the influence of Antibiotic Stewardship Strategies that have been implemented (Center for Disease Control and Prevention. National Center for Emerging and Zoonotic Infectious Diseases. 2015)(Sturm et al. 2007)(WHO Regional Office for Europe 2014)

The staying period significant associated with irrational drug use also the MDR development is significant associated with irrational drug use. Other factors show no significant association with irrationality. This result is similar to result done in Malaysia which was the rational treatment decrease the LOS in ICU and also the mortality(Al-Sunaidar, Abd Aziz, and Hassan 2020).

The DDD and DOD evaluates in our hospital during the last four years and there was different in the type that used, in turkey a study done to evaluate the DDD in different state showed that there are provincial and regional differences in antibiotic prescription which might be related with the distribution of infectious diseases and sociocultural differences. Assessment of antibiotic use is an important tool for preparing evidence-based strategies to spread the rational antibiotic use. The promotional activities must be put into practice by considering these regional and seasonal differences(“European Journal of Public Health, Vol. 26, Supplement 1, 2016” 2016).

Mortality is high in our hospital, and it associated with MDR development in our study, similar results showed by(Ailing, Huifang, and Qin 2018). Zilberberg et al in USA shows in his study that inappropriate antibiotic use double the mortality rate (Zilberberg et al. 2016). Another one by Gradel et al in Denmark This study showed that inappropriate antimicrobial treatment was a predictor of recurrent bacteremia and increased the long-term mortality following bacteremia(Gradel et al. 2017).

A study done by Danho Pascal Abrogoua highlight the role of the clinical pharmacist in inpatient management has contributed to the prevention and resolution of problems related to the pharmacotherapeutic management of TB (Abrogoua et al. 2016)

5.1. Strength and Limitations

It is the first study done to evaluate antibiotic use in ICU in Northern Cyprus and Turkey. However, the antibiotic utilization was identified and described, and antibiotics-associated problems were assessed, and its effect on mortality. The study involved four years duration and involved a relatively large sample of patients that include all patients who admitted to the ICU.

Nevertheless, the retrospective design of the study has many limitations. As much information is missing due to poor documentation, the reason for antibiotic initiation was not regularly documented, no patient progress note recorded, and no direct discussion with the prescriber, besides known limitations of such study designs. Patient discharge plans have not been registered, so antibiotic discharge was not involved

6. CONCLUSION AND RECOMMENDATION

In conclusion, the result obtained from our study shows that the rate of irrational antibiotic is high, especially with patients who need dose adjustment, de-escalation of antibiotic to narrower spectrum is a significant problem as the" time-out "concept is not applied in our hospital.

High consumption of broad-spectrum antibiotics for a long time associated with nosocomial infection, MDR development, which leads to an increase in LOS and mortality.

Poor documentation for antibiotic selection, the dose, the administration instruction, and the duration are considering another concern should be aware to avoid and control most of the problem.

Regarding the result obtained, we recommend implementing antibiotic stewardship program within the hospital will be adequate to decrease inappropriate and excessive use of antibiotics, optimize therapy and clinical outcomes for the infected patient and also it is imperative to provide education programs regarding the rational applications of antibiotics to all postgraduate student and antibiotic prescribers. Reassess the plane and the plan routinely and document the result to reach the optimum outcome.

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APPENDIX

Annex 1.

	eco	SAU		SCN	ECO	SAU	KPN	SEP	ABA	PAE	SMA	SPN	ENT
Amikacin	100.00%				100.00%		100.00%		0.00%	75.00%	100.00%	100.00%	100.00%
Amox-Clav	0.00%				0.00%		0.00%		0.00%		0.00%		0.00%
Amoxicillin	0.00%				0.00%		0.00%		0.00%		0.00%		50.00%
Aztreonam	40.00%				40.00%		0.00%		0.00%	50.00%	100.00%		100.00%
Cefepime	40.00%				40.00%		17.00%		0.00%	75.00%	100.00%		100.00%
Cefoxitin		0.00%		37.50%		0.00%		0.00%		0.00%			
Ciprofloxacin	20.00%	100.00%		25.00%	20.00%	100.00%	34.00%	0.00%	0.00%	50.00%	100.00%		50.00%
Colistin	100.00%				100.00%				100.00%	100.00%			
Daptomycin		100.00%		100.00%		100.00%		100.00%					
Clindamycin	0.00%	0.00%		48.50%	0.00%	0.00%		34.00%		0.00%		100.00%	0.00%
Erythromycin	100.00%			377.00%	100.00%					0.00%		100.00%	0.00%
Fosfomycin (IV)		100.00%				100.00%		0.00%					
Gentamicin	89.00%			85.00%	89.00%		67.00%	0.00%	0.00%	34.00%			50.00%
Imipenem	100.00%				100.00%		84.00%		0.00%	66.00%	0.00%		100.00%
Levofloxacin	100.00%			31.00%	100.00%		0.00%	0.00%	0.00%	0.00%		100.00%	100.00%
Linezolid				97.00%				100.00%		0.00%		100.00%	0.00%
Oxacillin				50.00%						0.00%			
Rif (comb)	100.00%			54.00%	100.00%					0.00%		100.00%	0.00%
Teicoplanin	100.00%			100.00%	100.00%					0.00%		100.00%	100.00%
Tetracycline	50.00%			71.00%	50.00%		100.00%	0.00%		0.00%		100.00%	0.00%
Tigecycline	100.00%			100.00%	100.00%		100.00%	34.00%	100.00%	100.00%		100.00%	
TMP-SMX	20.00%			29.00%	20.00%		34.00%	66.00%	0.00%	0.00%		100.00%	50.00%
Vancomycin	100.00%			100.00%	100.00%			100.00%		0.00%		100.00%	100.00%
Ceftriaxone	12.00%				12.00%		0.00%		0.00%	0.00%			100.00%
Cefurox-Axe	14.00%				14.00%		0.00%		0.00%				0.00%
Ertapenem	88.00%				88.00%		20.00%		0.00%	34.00%			100.00%
Meropenem	100.00%				100.00%		100.00%		0.00%	75.00%			100.00%
Netilmicin	67.00%				67.00%				0.00%				100.00%
Piperacillin	0.00%				0.00%								100.00%
Pip-Tazo	87.50%			100.00%	87.50%		84.00%		0.00%	75.00%			100.00%
Nitrofurantoin				100.00%									
Tobramycin									0.00%				
Ampicillin	100.00%				100.00%								
Ceftazidime	43.00%				43.00%		13.00%		0.00%	50.00%		100.00%	100.00%
Fusidic acid								0.00%					

Annex 2.

	unine		Amikacin	Gentamicin	Amox-Clav	Ampicillin	Aztreonam	Cefepime	Cefoxitin	Ciprofloxacin	Colistin	Daptomycin	Clindamycin	Erythromycin	Fosfomycin (IV)	Imipenem	Levofloxacin	Linezolid	Oxacillin	Rif (comb)	Teicoplanin	Tetracycline	Tigecycline	TMP-SMX	Vancomycin	Ceftriaxone	Cefuroxime	Ertapenem	Meropenem	PIPRACILLIN	Pip-Tazo	Nitrofurantoin	
ECO	E. coli (S)	42	96	100	15	0	20	17	100	0					89	100								45		23	0	100	77	82	78	21	21
ENT	Enterroco	7.5	50	50	0	0	100	100		34	0	100	0	0		100	0	100			100	50	100	34	100	100		100	100	100		100	100
SAU	S. aureus I	1.5		100					0	100			0		100		100	100			100	0	100	100	100						100		
eae	Enterobac	1.5	100	100	0	0	100	100		100						100										100		100	100	100		0	100
scn	Staph coag	1.5		100					100	100			0	100			100	100	100	100	100	0		100	100								
SAM	Serratia sp	1.5	0	100	0	0				100					100	100								100		100		100	100	100	0	0	100
ecl	Enterobac	1.5		100		0				0			0	0			0	100		0	100	0			100								
pae	P. aerugin	3	100	100			0	100		100	100					100												0	100	100			1
kpn	K. pneum	7.5	100	66	0	0	66	66	100	0					100	100								25		50	1	66	100	100	0	50	66
EFM	E. faecium	9.6		0		0				100								100			`	100	100	40	100								
EFA	E. faecalis	7.5		0		75												100			75		100	0	100								
ABA	A. baumar	7.5	34	0	0	0	0	0		0	100					0	0						100	0		0		0	0	0		0	0
PMI	P. mirabili	3	100	50	100	50	100	100	100	0						100								0		100		100	100	100	0	100	1

Annex 3.

aspira	aba	sep	pmi	ENT	SCN	PAE	KPN	SAU	SMA	EAE	ECO	ECL
Amikacin	11.00%		100.00%			83.00%	100.00%		100.00%	100.00%	83.00%	100.00%
Amox-Clav	79.00%		66.60%			0.00%	0.00%			0.00%	0.00%	0.00%
Amoxicillin	85.00%		0.00%			0.00%	0.00%			0.00%	0.00%	0.00%
Aztreonam	52.00%		100.00%			66.00%	15.00%		100.00%	100.00%	0.00%	100.00%
Cefepime	26.00%		100.00%			37.00%	15.00%		100.00%	50.00%	0.00%	0.00%
Cefoxitin						0.00%	100.00%	100.00%			0.00%	
Ciprofloxacin	10.00%	50.00%	34.00%	0.00%	0.00%	34.00%	25.00%	100.00%	0.00%	50.00%	0.00%	0.00%
Colistin	100.00%					100.00%	100.00%		0.00%			
Daptomycin		100.00%		100.00%	100.00%			100.00%				
Clindamycin		50.00%		0.00%	0.00%			100.00%				
Erythromycin		0.00%		0.00%	40.00%			50.00%				
Gentamicin	10.50%	50.00%	100.00%	0.00%	50.00%	100.00%	85.00%	75.00%	100.00%	100.00%	100.00%	100.00%
Imipenem	10.50%		100.00%			75.00%	100.00%			100.00%	100.00%	100.00%
Levofloxacin	0.00%	50.00%		0.00%	20.00%			100.00%	100.00%			
Linezolid		100.00%		100.00%	100.00%			100.00%				
Oxacillin		0.00%			0.00%			75.00%				
Rif (comb)		50.00%		0.00%	40.00%			100.00%				
Teicoplanin		100.00%		100.00%	100.00%			100.00%				
Tetracycline		50.00%		50.00%	80.00%			75.00%			100.00%	
Tigecycline	73.60%	100.00%	0.00%	100.00%		100.00%	85.00%			100.00%	100.00%	100.00%
TMP-SMX	52.00%	50.00%	34.00%		20.00%		57.00%	100.00%	0.00%	100.00%	80.00%	100.00%
Vancomycin		100.00%		100.00%	100.00%			100.00%				
Ceftriaxone	0.00%		100.00%			50.00%	20.00%		100.00%	100.00%	0.00%	100.00%
Cefurox-Axe			100.00%				10.00%				0.00%	
Ertapenem	0.00%		100.00%			15.00%	30.00%			100.00%	75.00%	100.00%
Meropenem	0.00%		100.00%			55.00%	90.00%		100.00%	100.00%	100.00%	
Netilmicin	0.00%		50.00%			100.00%	30.00%			100.00%		100.00%
Piperacillin			100.00%									
Pip-Tazo	0.00%		100.00%			75.00%	55.00%			100.00%	66.00%	100.00%
Nitrofurantoin	0.00%	50.00%										
Cefixime	0.00%											
Tobramycin	25.00%	50.00%										
Ceftazidime	7.00%		100.00%			8.00%	20.00%		100.00%	100.00%	0.00%	100.00%