TAMARA PERPETUAL UCHE NWOKOLO

CO-RESISTANCE OF EXTENDED SPECTRUM BETA LACTAMASE (ESBL) PRODUCING AND

M.Sc.

2023

NEAR EAST UNIVERSITY

INSTITUTE OF GRADUATE STUDIES

DEPARTMENT OF MEDICAL MICROBIOLOGY

AND CLINICAL MICROBIOLOGY

CO-RESISTANCE OF EXTENDED SPECTRUM BETA LACTAMASE (ESBL) PRODUCING AND QUINOLONE RESISTANCE AMONG GRAM-NEGATIVE ENTERIC BACTERIA STRAINS IN CLINICAL SAMPLES IN TRNC.

M.Sc. THESIS

TAMARA PERPETUAL UCHE NWOKOLO

Nicosia

June, 2023

NEAR EAST UNIVERSITY
INSTITUTE OF GRADUATE STUDIES
DEPARTMENT OF MEDICAL MICROBIOLOGY
AND CLINICAL MICROBIOLOGY

CO-RESISTANCE OF EXTENDED SPECTRUM BETA LACTAMASE (ESBL) PRODUCING AND QUINOLONE RESISTANCE AMONG GRAM-NEGATIVE ENTERIC BACTERIA STRAINS IN CLINICAL SAMPLES IN TRNC.

M.Sc. THESIS

TAMARA PERPETUAL UCHE NWOKOLO

Supervisor
Prof. Dr. Nedim Cakir

Nicosia
June, 2023

Approval

We certify that we have read the thesis submitted by TAMARA PERPETUAL UCHE NWOKOLO titled **"CO-RESISTANCE OF EXTENDED SPECTRUM BETA LACTAMASE (ESBL) PRODUCING AND QUINOLONE AMONG GRAM NEGETIVE BACTERIA STRAINS IN CLINICAL SAMPLES IN TRNC"** and that in our combined opinion it is fully adequate, in scope and in quality, as a thesis for the degree of Master of Educational Sciences.

Examining Committee	Name-Surname	Signature
Head of the Committee:	Prof. Dr. Kaya Suer	.....
Committee Member*:	Assistant Prof. Hulya Arik	.....
Supervisor:	Prof. Dr. Nedim Cakir	.....

Approved by the Head of the Department

26/06/2023

.....

Prof. Dr. Nedim Cakir

Head of Department

Approved by the Institute of Graduate Studies

...../20...

Prof. Dr. Kemal Hüsnü Can Başer

Head of the Institute

Declaration

I hereby declare that all information, documents, analysis and results in this thesis have been collected and presented according to the academic rules and ethical guidelines of Institute of Graduate Studies, Near East University. I also declare that as required by these rules and conduct, I have fully cited and referenced information and data that are not original to this study.

TAMARA PERPETUAL UCHE NWOKOLO

…../…../…..

Acknowledgments

My utmost gratitude goes to God Almighty for his provision and direction during this academic pursuit. As well as for granting me the fortitude, perseverance and knowledge necessary for my research work.

I want to thank my M.Sc. supervisor, Prof. Dr. Nedim Cakir and convey my profound gratitude for all his assistance also for painstaking taking his time to advice and guidance which led me in the right route and was particularly important to the success of this study.

Special and unreserved thanks to my amazing family especially my mom for the endless support, encouragements and making sure I lacked nothing during the course of this academic journey.

To my friends Chris, Chima and Eney, I appreciate all your contribution and support to completion of research work. To my girls - Mine, Deji and Gabby. You all have been my strong support even from miles away. I cannot quantify how grateful I am to have all of you in my life and corner. Thanks a lot guys.

Tamara Perpetual Uche Nwokolo

Abstract

CO-RESISTANCE OF EXTENDED SPECTRUM BETA LACTAMASE (ESBL) PRODUCING AND QUINOLONE AMONG GRAM NEGETIVE BACTERIA STRAINS IN CLINICAL SAMPLES IN TRNC.

NWOKOLO TAMARA PERPETUAL UCHE

M.Sc, Department of Medical Microbiology

And Clinical Microbiology.

June, 2023, 114 pages.

Enterobacteriaceae are a family of gram-negative bacteria that bacilli are typically 1.5μm in length. They are found in the human intestinal tract and are a part of the gut microbiota. Others can be found in water, soil or different plants and animals. They are opportunistic pathogen that cause nosocomial infections. ESBLs possess the capability to degrade β-lactam, granting them resistance against a broad spectrum of β-lactam antibiotics, including penicillins and Cephalosporins. Quinolone antibiotics are synthetic antibacterial agent that are broad-spectrum bactericidal agents effective against some Gram positive and Gram negative bacteria. Their primary and secondary targets of DNA gyrase and topoisomerase IV respectively thereby disrupting DNA replication. The aim of this study was to identify co-resistance ESBL producing and quinolone resistance among gram-negative enteric bacteria strains in clinical samples hospital, compare and evaluate different phenotypic methods currently in use. This cross sectional observational study was conducted from 11th June 2020 - 6th June 2022 at the Near East University Hospital Nicosia, Northern Cyprus. A total of 287 ESBL isolates from OPD, ICU, CCU etc departments were analyzed during this period. To accomplish this, we compared and evaluated the phenotypic analysis using the automated vitek2 system and BD Bactec machine. The use of two microbiological media, Blood agar and EMB agar, made the two approaches easier to analyze. From the three microorganism isolated and analyzed, *E coli* was most prevalent (64.8%), followed by *K pneumonia* (32.8%) and *P mirabilis* 2.4%. Inpatient had 59.2% antibiotic resistance compared to outpatient 40.8%. The most susceptibile antibiotics were fosfomycin and imipenem 92.3% and 89.8% respectively. In addition, fosfomycin and imipenem are the best choice of antibiotics used for the treatment of ESBL producing strain.

Keywords: extended spectrum beta lactamase, penicillin, quinolone, enterobacteriacea, phenotypic**.**

Özet

KKTC'DEKİ KLİNİK ÖRNEKLERDEKİ GRAM NEJETİF BAKTERİ SUŞLARINDAN GENİŞLETİLMİŞ SPEKTRUMLU BETA LAKTAMAZ (ESBL) ÜRETİCİSİ İLE KİNOLONUN ORTAK DİRENCİ.

NWOKOLO TAMARA SÜREKLİ UCHE

Yüksek Lisans, Tıbbi Mikrobiyoloji Anabilim Dalı

Ve Klinik Mikrobiyoloji.

Haziran 2023, 114 sayfa.

Enterobacteriaceae, basillerin tipik olarak 1,5 µm uzunluğunda olduğu bir gram-negatif bakteri ailesidir. İnsan bağırsak sisteminde bulunurlar ve bağırsak mikrobiyotasının bir parçasıdırlar. Diğerleri suda, toprakta veya farklı bitki ve hayvanlarda bulunabilir. Nozokomiyal enfeksiyonlara neden olan fırsatçı patojenlerdir. ESBL'ler, β-laktamı parçalama yeteneğine sahiptir ve onlara penisilinler ve Sefalosporinler dahil olmak üzere geniş bir β-laktam antibiyotik yelpazesine karşı direnç kazandırır. Kinolon antibiyotikler, bazı Gram pozitif ve Gram negatif bakterilere karşı etkili olan geniş spektrumlu bakterisidal maddeler olan sentetik antibakteriyel maddelerdir. Sırasıyla DNA giraz ve topoizomeraz IV'ün birincil ve ikincil hedefleri, böylece DNA replikasyonunu bozar. Bu çalışmanın amacı klinik numune hastanesindeki gram-negatif enterik bakteri suşları arasında ko-direnç GSBL üreten ve kinolon direncini belirlemek, halihazırda kullanımda olan farklı fenotipik yöntemleri karşılaştırmak ve değerlendirmektir. Bu kesitsel gözlemsel çalışma 11 Haziran 2020 - 6 Haziran 2022 tarihleri arasında Kuzey Kıbrıs'ta Yakın Doğu Üniversitesi Hastanesi Lefkoşa'da yapılmıştır. Bu süre zarfında OPD, YBÜ, CCU vb. bölümlerinden toplam 287 GSBL izolatı analiz edildi. Bunu başarmak için otomatik vitek 2 sistemi ve BD Bactec makinesini kullanarak fenotipik analizi karşılaştırdık ve değerlendirdik. Blood agar ve EMB agar olmak üzere iki mikrobiyolojik ortamın kullanılması, iki yaklaşımın analiz edilmesini kolaylaştırdı. İzole edilen ve analiz edilen üç mikroorganizma arasında en yaygın olanı *E coli* (%64,8), ardından *K pnömoni* (%32,8) ve *P mirabilis* (%2,4) geldi. Yatan hasta %59,2 antibiyotik direncine sahipken, ayaktan hasta %40,8 idi. En duyarlı antibiyotikler sırasıyla %92,3 ile fosfomisin ve %89,8 ile imipenem olmuştur. Ayrıca fosfomisin ve imipenem GSBL üreten suşların tedavisinde kullanılan en iyi antibiyotik seçenekleridir.

Anahtar Kelimeler: genişletilmiş spektrumlu beta laktamaz, penisilin, kinolon, enterobakteriler, fenotipik.

Table of Contents

CHAPTER I

CHAPTER II

List of Tables

List of Figures

List of Abbreviations

TRNC:	Turkish Republic of North Cyprus
%:	Percentage
µg:	Micro gram
µl:	Micro liter
HCAIs:	Healthcare-Associated Infection
CLSI:	Clinical and Laboratory Standards Institute
DNA:	Deoxy Ribonucleic Acid
ESBL:	Extended Spectrum Beta Lactamase
PICU:	Pediatric Intensive Care Unit
VAP:	Ventilator-Associated Pneumonia
MDR:	Multi Drug Resistant
MHA:	Muller Hinton Agar
MIC:	Minimum Inhibitory Concentration
eCDC:	European Center for Disease Prevention and Control
PCR:	Polymerase Chain Reaction
pH:	Power of Hydrogen
HIV:	Human Immunodeficiency Virus
AIDS:	Acquired Immunodeficiency Syndrome
XDR:	Extremely Drug Resistant
ICU:	Intensive Care Unit
FQ:	Fluoroquinolones
AAC:	Aminoglycoside Acetyltransferase
ANT:	Aminoglycoside Adenyl transferase
PBP:	Penicillin-binding Protein
MHT:	Modified Hodge Test
RND:	Resistance-Nodulation-Division
β:	Beta
AMK:	Amikacin
AMX-CA:	Amoxicillin/Clavulanate
AMP:	Ampicillin
ATM:	Aztreonam
CEZ:	Cefazolin

CFP:	Cefepime
CFX:	Cefixime
CXT:	Cefoxitin
CAZ:	Ceftazidime
CRO:	Ceftriaxone
CXM-AX:	Cefuroxime-axetil
CIP:	Ciprofloxacin
CST:	Colistin
ETP:	Ertapenem
FOF:	Fosfomycin
GN:	Gentamicin
IMP:	Imipenem
LFX:	Levofloxacin
MEM:	Meropenem
NLT:	Netilmicin
NFT:	Nitrofurantoin
TPZ:	Piperacillin/Tazobactam
PPR:	Piperacillin
TGC:	Tigecycline
TBM:	Tobramycin
SXT:	Trimethoprim/Sulfamethoxazole
µl:	Micro liter
µl:	Micro liter
µg:	Micro gram
µl:	Micro liter
µg:	Micro gram
µl:	Micro liter

CHAPTER ONE.

Introduction.

Paul Ehrlich coined the term "magic bullets" to describe antimicrobial agents, which are capable of killing microbes.[1] For many years, these magic bullets have been successfully used to treat bacterial infections, leading to Ehrlich being awarded the Nobel Prize. Antibiotic misuse has given rise to antimicrobial resistance, a major worldwide public health concern in recent years.[2-3] Reports indicate that around 650,000 people die annually due to antimicrobial resistance (AMR) infections, with predictions suggesting that this number could increase to 10 million by 2050.[4]

ESBLs possess the capability to degrade β-lactam, granting them resistance against a broad spectrum of β-lactam antibiotics, including penicillins, first, second, third, and fourth-generation Cephalosporins, and aztreonam. Nevertheless, ESBLs are susceptible to inhibition by β-lactamase inhibitors, such as clavulanic acid, Tazobactam, and Sulbactam. However, Carbapenems, Cephamycins, and Moxalactam remain effective against them.[5-6] Additionally, organisms that produce ESBLs may also become resistant to some other types of β-lactam antibiotics, such as Aminoglycosides, Quinolones and Trimethoprim sulfamethoxazole.[7-8]

Many Gram-negative bacteria, including Escherichia, Klebsiella, and Proteus of the Enterobacteriaceae family, as well as Pseudomonas aeruginosa and Acinetobacter baumannii, utilize β-lactamase enzymes to degrade β-lactam antibiotics, making this the primary mechanism of resistance against them.[9-10] ESBL enzymes produced by these organisms make these antibiotics ineffective in treating infections, thereby increasing morbidity, mortality and the cost of therapy.[11]

Quinolone antibiotics are a class of potent broad-spectrum bactericidal agents that possess a bicyclic core structure related to the substance 4-quinolone.[12] They are used to treat bacterial infections in both human and veterinary medicine, as well as in animal husbandry, especially in poultry production. Fluoroquinolones, which include a fluorine atom in their chemical composition, constitute the majority of quinolone antibiotics currently utilized and possess activity against both Gram negative and Gram positive bacteria. One frequently prescribed fluoroquinolone antibiotic is ciprofloxacin.[13]

Currently, β-lactam drugs are a crucial component of bacterial infection treatment worldwide, comprising nearly 65% of all antibiotic usage.[14] The structure of

the β-lactam ring categorizes them into six primary groups, which are Penicillin, Cephalosporin, Cephamycins, Carbapenems, Monobactams, and β-lactamase inhibitors. These medications disrupt cell wall synthesis by inhibiting the normal operation of Penicillin binding protein (PBP), a crucial participant in bacterial cell wall synthesis, leading to bacterial demise. Nonetheless, there has been a growing global trend of resistance to this critical antibiotic class in recent years.[15]

Antibiotic resistance can arise from various mechanisms, including the development of efflux pumps, modifications in outer membrane porin production, changes in PBPs, and the generation of β-lactamase, which can deactivate antibiotics. Among these, β-lactamase production is the most prevalent reason for resistance to β-lactam antibiotics, which can be generated by both Gram-positive (extracellularly) and Gram negative bacteria. By binding covalently to the carbonyl section of β-lactam antibiotics and hydrolyzing the β-lactam ring, these enzymes can render them inactive leading to β-lactam resistance.[15-16]

Extended Spectrum Beta Lactamases belong to AMBLER class and utilize serine for all β-lactam hydrolysis except Carbapenems and Cephamycin.[17]

Although β-lactamases are naturally occurring in some bacteria, they have become widespread as a result of their mobilization on plasmids, transposons, insertion sequences, integrons, and bacteriophages. Mobile genetic elements (MGEs) offer the dissemination of ESBL-encoding genes, which often harbor resistance genes to other antimicrobial classes. The overuse of β-lactam antibiotics has contributed to this phenomenon. Mobile genetic elements (MGEs) facilitate the transfer of genes within a cell or between cells horizontally, via conjugation, transformation, or transduction by bacteriophages. These MGEs frequently harbor several resistance genes that bestow a multidrug-resistant characteristic to the organisms that host them.[18]

ESBL-encoding genes, being plasmid-mediated, can easily exchange not only within the same bacterial group but also across different species. For instance, ESBL genes present in *E coli* can be transferred to Klebsiella, Pseudomonas, or even gram-positive bacteria. Furthermore, the plasmid location of ESBL genes contributes to their horizontal spread within the same bacterial species and to other species, resulting in the production of genes that encode resistance to various classes of antibiotics such as aminoglycosides, quinolones, and others. This severely limits the treatment options for ESBL-producing organisms, thereby posing a significant threat to successful treatment.[19]

The prevalence of ESBL is influenced by various factors, including the bacterial species, geographical location, hospital settings, patient groups, and the type of infection. Additionally, the extensive misuse and overuse of these antibiotics leads to the emergence and spread of ESBL[20-21] While Klebsiella pneumoniae and Escherichia coli are the primary ESBL-producing bacteria worldwide, ESBL enzymes can be identified in other Enterobacteriaceae family members as well as certain non-fermenting bacteria. The presence of ESBL-producing bacteria can lead to a diverse range of infections, varying from simple urinary tract infections, diarrhea, and skin infections to severe life-threatening conditions, such as septic shock, pneumonia, gastroenteritis, and nosocomial infections.[22]

ESBL-producing organisms can be transmitted in both clinical and community settings through direct contact with bodily fluids such as blood, wound drainage, urine, and phlegm of an infected individual. They can also be spread through contact with contaminated equipment or surfaces, such as catheters or surgical instruments, as well as through contaminated hands.

1.1 Statement of Problem.

An analysis has been conducted on ESBL and Quinolone. ESBL is one form of Gram-negative bacterium that may lead to infections in humans, animals, and plants. Antibiotic resistance in Enterobacteriaceae has become a major concern globally in the last decade, despite the widespread use of β-lactams as the primary treatment for severe infections caused by these bacteria.[23] Therefore, developing a suitable investigation into the co-resistance of ESBL and Quinolone among Gram-negative bacterial strains is crucial to obtaining a desirable outcome. Previous knowledge and experience in creating a reasonable explanatory arrangement can have an important impact in assisting in the analysis.

1.2 Justification.

Various studies have shown ESBL and quinolone activity. However, little is done on the Co-resistance of ESBL producing and quinolone resistance among gram-negative enteric bacteria strains in clinical samples in Turkish Republic of Northern Cyprus (TRNC). The objective of this study is to examine the co-resistance of ESBL-producing and quinolone resistance among gram-negative enteric bacteria strains in clinical samples in TRNC.

1.3 Purpose of the Study

The purpose of this study was to identify co-resistance ESBL producing and quinolone resistance among gram-negative enteric bacteria strains in clinical samples hospital, compare and evaluate different phenotypic methods currently in use.

To identify the fluoroquinolone resistance among ESBL producing gram-negative enteric bacteria strains in clinical samples in hospital settings, to assist clinicians for easy and correct drug of choice.

1.4 Intended Outcome of Thesis/Significance

To determine anti-biograms that will guide clinicians in prescribing proper antibiotic and controlling hospital infections.

1.5 Limitation of Study

This research work is limited to the investigation of the Co-resistance of ESBL producing and quinolone resistance among gram-negative enteric bacteria strains in clinical samples.

1.6 Scope of Study

The study was carried out on isolates gotten from Near East University Teaching Hospital, to identify and investigate the Co-resistance of ESBL producing and quinolone resistance among gram-negative enteric bacteria strains.

1.7 Area of Study

This research work was carried out in the microbiological laboratory of Near East University, TRNC.

CHAPTER TWO

Literature Review

2.1 Enterobacteriaceae

The family of gram-negative bacteria known as Enterobacteriaceae was first proposed by Rahn in 1936 and has since grown to include over 30 genera and more than 100 species.[24] While some classifications place it in the order Enterobacterales of the class Gammaproteobacteria in the phylum Pseudomonadota.[25-28] In 2016 the family's description and members were modified based on comparative genomic investigations.[29] These bacilli are typically 1.5μm in length and appear as medium to large sized grey colonies on blood agar, although some can express other pigments. Salmonella, Klebsiella, Escherichia coli, Proteus, Shigella, Citrobacter, and other species are among the pathogens in this family, many of which are found in the human intestinal tract and are a part of the gut microbiota.[30] Others can be found in water or soil or can be parasites on a variety of different plants and animals.[31] However, the classification of this family above the level of family is still a topic of debate.

Enterobacteriaceae are commonly motile bacteria, propelled by flagella, although there are some genera that are non-motile. Petrichous type 1 fimbriae are used by most Enterobacteriaceae for adhesion to their host cell.[32] They are gram-negative pseudomonadota and are facultative anaerobes. They ferment sugar to produce lactic acid and other end products, and some are capable of reducing nitrate to nitrite.[33] The presence of cytochrome c oxidase and catalase reactions vary among Enterobacteriaceae. These bacteria are well-known for producing endotoxins that are contained in their cell walls and are released upon cell lysis. Certain Enterobacteriaceae can produce endotoxins that cause a systemic inflammatory and vasodilatory response when released into the bloodstream, with the most severe form being endotoxin shock which can be deadly.[31]

2.2 *Escherichia Coli*

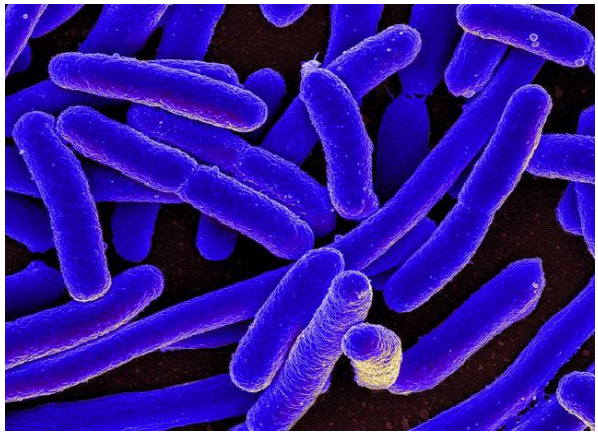
The bacterium known as Escherichia coli (*E coli*) was first identified by Theodor Escherich, a German pediatrician and bacteriologist in 1885.[34] *E coli* is a bacterium that has a rod-shaped, gram-negative structure, and it can function as a facultative anaerobe. Its size can be measured as approximately 2.0 μm in length and 0.25 μm-1.0 μm in diameter, with a total volume of 0.6 μm-0.7 μm.[35] It is a member of the coliform group of bacteria and possesses a flagellum with a petrichous arrangement that allows it to swim.[36] *E coli* attaches to and effaces the microvilli of

the intestine using an adhesion molecule called intimin. *E coli* is typically present in the lower intestine of warm-blooded organisms. Although the majority of *E coli* strains are benign, certain serotypes can be pathogenic and pose a threat to the host's health.

Around 0.1% of the human gut microbiota comprises harmless *E coli* strains and other facultative anaerobes, which can be beneficial to their host by producing vitamin K2 and preventing colonization of the intestine by pathogenic bacteria, thus establishing a mutualistic relationship.[37-38] However, pathogenic *E coli* strains produce toxins and other virulence factors that enable them to inhabit parts of the body not normally colonized by *E coli* and cause damage to the host cells.[39] The genes responsible for pathogenicity are carried exclusively by the virulence genes of these pathogens and are not found in normal *E coli* strains.

Figure 1

E coli under the microscope, gram stain technique- hanging drop method.[40]



2.2.1 E coli Mode of Transmission

The primary mode of transmission for pathogenic strains of the bacterium is through fecal-oral contact.[41] This can occur via various means, including unhygienic food preparation, agricultural contamination from manure fertilizer, irrigation of crops with polluted greywater or raw sewage,[42] feral pigs on farms,[43] ingestion of sewage-infected water,[44] and other routes. Cattle, especially dairy and beef cattle, are significant carriers of *E coli* O157:H7 and can shed it in their feces without displaying symptoms.[45] Food products such as cucumber, raw ground beef, raw seed sprouts or spinach,[46] raw milk, unpasteurized juice, unpasteurized cheese, and food contaminated by ill food workers through the fecal-oral pathway have all been associated with *E coli* outbreaks.

According to the U.S. Food and Drug Administration, several measures can be taken to break the fecal-oral cycle of transmission. These include pasteurizing juice or dairy products, following proper hand washing guidelines, properly cooking food, preventing cross-contamination, and implementing health care policies so that food industry employees seek treatment when they are ill. Additionally, instituting barriers like gloves for food workers can also be effective. Testing environmental samples for fecal contamination is often done using indicator organisms since cells are only able to survive outside the body for a limited amount of time, making them ideal for this purpose.[34]

The characteristics that trigger an immune response can be used to classify pathogenic *E coli* strains.

- O antigen: This is the outer membrane of an *E coli* cell which contains millions of lipopolysaccharide(LPS) molecules they consist of;
  - O antigen, a polymer of immunogenic repeating oligosaccharides (1-40 units)
  - Core region of phosphorylated non-repeating oligosaccharides
  - Lipid A also known as endotoxin.[25]
- K antigen: The acidic capsular polysaccharide (CPS) is a thick, mucous-like, layer of polysaccharide that surrounds some pathogen *E coli*. There are two separate groups of K-antigen groups, named group I and group II.

  Group I K antigens are only found with certain O-antigens (O8, O9, O20, and O101 groups), they are further subdivided on the basis of presence of amino sugars and some group I K-antigens are attached to the lipid A-core of the lipopolysacc haride (K_{LPS}), in a similar way to O antigens.[25]

  Group II K antigens closely resemble those in gram positive bacteria and greatly differ in composition and are further subdivided according to their acidic components.

  Generally, 20–50% of the capsular polysaccharide (CPS) chains are bound to phospholipids. In total there are 60 different K antigens that have been recognized.
- H antigen: The H antigen is a major component of flagella, involved in *E coli* movement. It is generally encoded by the *fliC* gene. There are 53 identified H antigens, numbered from H1 to H56 (H13 and H22 were not *E coli* antigens but from *Citrobacter freundii* and H50 was found to be the same as H10).[47]

2.2.2 Features of Virulence:

Based on their virulence traits and serological traits, enteric *E coli* (EC) are categorized.[48] Below are a list of the main *E coli* pathotypes that cause diarrhea.

- *Enterotoxigenic E coli* (*ETEC*): Causes diarrhea without fever in both humans and animals. The intestinal lumen is not left behind by ETEC strains, making them noninvasive. ETEC is the most prevalent bacterial cause of traveler's diarrhea and the primary bacterial cause of diarrhea in children in poor countries. ETEC is thought to affect 840 million people annually in poor nations. The majority of these cases about 280 million and 325,000 deaths affect children under the age of five.[49]
- *Enteropathogenic E coli (EPEC*): Causes of diarrhea in people and animals. EPEC induces diarrhea, although the aetiology and colonization molecular processes are distinct. Although EPEC lack ST and LT toxins, they attach host intestinal cells using an adhesin called intimin. A variety of virulence factors present in this pathotype are comparable to those in Shigella. Actin in the host cell is rearranged as a result of adhesion to the intestinal mucosa, significantly deforming the cell. Invading host cells with a modest degree of invasiveness, EPEC cells cause an inflammatory reaction. In those with EPEC, changes in intestinal cell ultrastructure brought on by "attachment and effacement" are probably the main cause of diarrhea.
- *Enteroaggregative E coli (EAEC)*: This is exclusively found in humans causing watery diarrhea. EAEC are so-called because they attach to the intestinal mucosa and induce watery diarrhea without a fever. They have fimbriae that gather tissue culture cells. EAEC don't do any harm. They generate an ETEC-like hemolysin and a ST enterotoxin.
- *Enteroinvasive E coli (EIEC)*: Only humans carry this bacteria which causes either bloody or non-bloody diarrhea. Shigellosis-like symptoms, including excessive diarrhea and a high temperature, are brought on by EIEC infection.
- *Enterohemorrhagic E coli (EHEC)*: This is mostly found in humans and animals either bloody or non-bloody. The pathotype's most notorious member, strain O157:H7, is known for its violent diarrhea and lack of fever. Hemolytic uremic syndrome and unexpected renal failure can be brought on by EHEC. It is fairly invasive, employs bacterial fimbriae for attachment (*E coli* common pilus, ECP[50] and has a phage-encoded shiga toxin that can cause a significant inflammatory reaction.
- *Adherent-Invasive E coli (AIEC):* This is only found in humans. AIEC may enter intestinal epithelial cells and carry out intracellular replication. It is believed that hosts

with compromised innate immunity are more conducive to AIEC proliferation. When someone has Crohn's disease[51] and they are connected to the ileal mucosa.

- *In addition Shiga toxin-producing E coli (STEC)*; notably serotype O157:H7, have been transmitted by flies[52-54] and also close contact with farm animals, petting zoo animals[55] and airborne particles common in animal-rearing facilities.[56]

2.2.3 *E coli* Associated Diseases.

2.2.3.1 Gastrointestinal Infection.

Some strains of *E coli* produce potentially fatal toxins, causing food poisoning that can be contracted by eating unclean or undercooked vegetables or improperly slaughtered and undercooked meat. The O157:H7 strain is infamous for producing severe and sometimes fatal side effects, such as hemolytic-uremic syndrome.[57] In 2006, a fresh spinach-related *E coli* epidemic occurred in the United States and was associated with this specific strain. Another highly dangerous strain is O104:H4, which has less defined antibiotic and supportive therapy procedures. This strain can be very enterohemorrhagic, causing bloody diarrhea, but it is also more enteroaggregative, meaning it adheres well and clumps to intestinal membranes. In June 2011, this strain caused a catastrophic *E coli* epidemic in Europe. While the infection is typically moderate, it can be deadly, especially for small children, the elderly, or those with impaired immune systems.

E coli has the ability to generate two kinds of enterotoxins: heat-stable and heat-labile. The heat-labile toxins are structurally and functionally similar to cholera toxins and comprise one A subunit and five B subunits that together form a holotoxin. The A subunit acts by cleaving and inhibiting the absorption of water by cells, which causes diarrhea, while the B subunits aid in the attachment and entry of the toxins into the host's intestinal cells. The heat-labile toxins are secreted via the Type 2 secretion pathway.[58] They typically cause peritonitis, which can be fatal if not treated, when they escape the intestinal wall through a hole caused by an ulcer, a ruptured appendix, or a surgical error, and enter the abdominal cavity. Fortunately, drugs such as streptomycin or gentamicin are quite effective against *E coli* Nonetheless, recent research indicates that treating enteropathogenic *E coli* with antibiotics may not modify the course of the disease and could significantly raise the risk of developing hemolytic-uremic syndrome.[59]

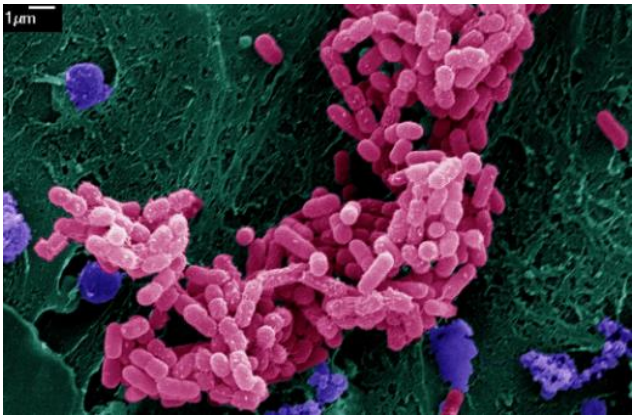
A conducted research indicated a correlation between elevated levels of *E coli* in the intestinal mucosa and inflammatory bowel diseases like Crohn's disease and ulcerative colitis.[60] It was also found that the presence of invasive *E coli* strains in inflamed tissue and the amount of bacteria present are linked to the severity of intestinal inflammation.[61] Furthermore, the body may produce memory T cells to fight bacteria in the gastrointestinal tract in response to gastrointestinal diseases. Researchers[62] have suggested that the immune system may respond to gut bacteria following food poisoning, potentially leading to inflammatory bowel disease.

2.2.3.2 Urinary Tract Infection

2.2.3.2.1 ***Uropathogenic E coli (Upec)***: This is responsible for around 90% of urinary tract infections (UTI) in people with typical anatomy.[48] Fecal bacteria colonize the urethra in ascending infections, moving up the urinary canal to the bladder, kidneys producing pyelonephritis[63] or in men, the prostate. Women are 14 times more likely than males to have an ascending UTI due to the shorter urethra in women.[48]

Figure 2

E coli bacteria growing on mini-guts[64]



P fimbriae (pyelonephritis-associated pili) are used by uropathogenic *E coli* to bind urinary tract urothelial cells and colonize the bladder. The uroepithelial cells are selectively bound by these adhesins.[48] This receptor is only present in around 1% of people and whether it is present or not determines whether a person is susceptible to *E coli* urinary tract infections. Alpha (α) and beta (β) hemolysins, which are produced by uropathogenic *E coli* and induce the lysis of urinary tract cells.

The Dr family of adhesins, which are notably linked to cystitis and pregnancy-associated pyelonephritis,[65] is another virulence factor that is frequently present in

UPEC. The Dr adhesins bind the Dr blood group antigen (Dra), which is found on erythrocytes and other cell types as decay accelerating factor (DAF). There, the Dr adhesins trigger a number of signal transduction cascades, including activation of PI-3 kinase, as well as the growth of lengthy cellular extensions that encircle the bacterium.[63]

By infiltrating superficial umbrella cells to create intracellular bacterial populations (IBCs), UPEC can circumvent the body's innate immune defenses such as the complement system.[66] They can also produce K antigen, a kind of capsular polysaccharide that aids in the development of biofilms. *E coli* that produces biofilms is resistant to immunological stimuli and antibiotic treatment and it frequently causes chronic urinary tract infections.[67] Upper urinary tract infections are caused by *E coli* that produce K antigen which are rather prevalent.

Despite being extremely uncommon, descending infections can occur when *E coli* cells go from the bloodstream to the upper urinary system organs such as kidneys, bladder or ureters.[48]

2.2.3.3 Neonatal Meningitis (NMEC)

The K1 capsular antigen, produced by a specific *E coli* serotype, is responsible for causing bacteremia in newborns. This strain is commonly found in the mother's vaginal area and can colonize the intestines of the newborns, leading to meningitis. Due to the absence of IgM antibodies from the mother,[68] the K1 antigen is mistakenly identified by the infant's body as its own due to its similarity to cerebral glycopeptides, ultimately leading to severe meningitis.

2.2.3.4 Colorectal Cancer

Certain strains of *E coli* contain a genomic island called a polyketide synthase (pks), which encodes a multi-enzymatic system capable of producing colibactin, a compound that can damage DNA. Approximately 20% of individuals have *E coli* colonies that carry the Pks Island.[69] Colibactin has been linked to the development of cancer[70] and cellular senescence[71] by causing DNA damage. However, *E coli* is unable to penetrate the mucosal barrier and reach the surface of enterocytes. Inflammatory conditions, which reduce mucin synthesis,[72] are necessary for the bacteria to transport colibactin to enterocytes and cause tumorogenesis.[73]

2.2.3.5 Diseases in Animals

Various viral strains of *E coli* in animals have been linked to several illnesses, including sepsis and diarrhea in newborn calves, acute mastitis in dairy cows, and colibacillosis,[74] which is associated with chronic respiratory disease in poultry caused by Mycoplasma. This disease can result in perihepatitis, pericarditis, septicaemic lungs, peritonitis, and other complications. In addition, *E coli* is responsible for Alabama rot in dogs and other illnesses. Although most poultry serotypes are only harmful to birds, the source of *E coli* in birds is not considered a significant cause of infections in other animals. In fewer instances, virulent strains can also cause gram-negative pneumonia, peritonitis, mastitis, septicemia and hemolytic uremic syndrome.

2.3 Klebsiella Pneumoniae

Klebsiella, a genus of bacteria, was named in honor of German scientist Edwin Klebs (1834-1913), who discovered the bacteria in the airways of people who died from pneumonia in 1875. It is also referred to as Friedländer's bacillus after German pathologist Carl Friedländer (1882), who postulated that this bacteria was the cause of pneumonia. It is most common in immunocompromised individuals, including those with chronic illnesses, alcoholism, or diabetes mellitus. Klebsiella pneumoniae, the strain responsible for community-acquired pneumonia,[75] is a rod-shaped, gram-negative, non-motile, encapsulated, facultatively anaerobic, lactose-fermenting bacteria that appears as a mucoid lactose fermenter on MacConkey agar. Although it is part of the normal flora of the mouth, skin, and intestines,[76] it can cause harm to human and animal lungs when inhaled, as it colonizes the oropharynx and gastrointestinal (GI) tract mucosa of humans. Magill et al (2014)[77] have reported that *E coli* is responsible for various infections in humans such as respiratory tract infections, urinary tract infections (UTIs), intra-abdominal infections, meningitis, pyogenic liver abscesses, and bloodstream infections. If aspirated, it can damage the alveoli, resulting in crimson, brownish, or yellow sputum that resembles jelly, and it exhibits significant levels of pathogenicity and antibiotic resistance once it enters the host.

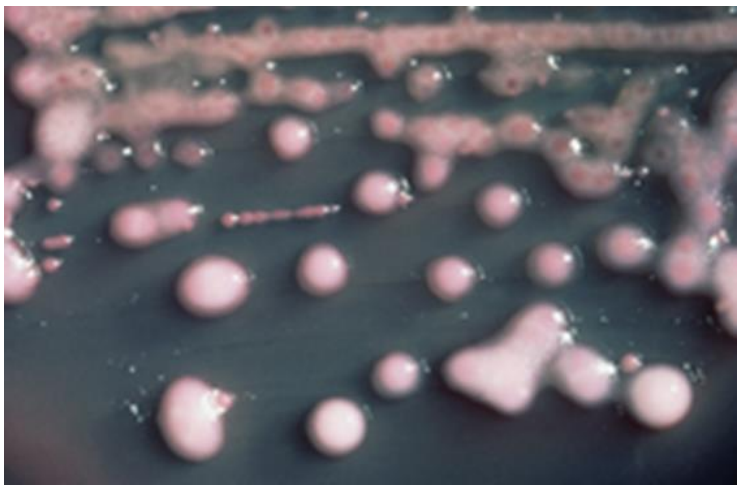
It is the most important member of the Enterobacteriaceae genus *Klebsiella* in the clinical context. Clinical samples from humans have also shown the presence of *K oxytoca* and *K rhinoscleromatis*. Klebsiella species are now recognized as significant nosocomial infection pathogens, and in the United States, they have been identified as

the third most common cause of healthcare-associated infections (HAIs) at 9.9%, after Clostridium difficile and Staphylococcus aureus.[77]

About 30% of the strains can fix nitrogen under anaerobic circumstances and they are found in the soil where it naturally exists. As a free-living diazotroph, *K pneumoniae's* nitrogen-fixation mechanism has undergone extensive study and is of agricultural importance since it has been shown to boost crop yields in agricultural settings.[78]

Figure 3

K pneumoniae on MacConkey agar.[79]



2.3.1 Virulence Factors

The most significant virulence factor possessed by Klebsiella pneumoniae is its complex acidic polysaccharide capsule, which protects it from opsonophagocytosis and serum death by the host organism. There are currently 77 identified capsular forms, and Klebsiella species that lack capsules are generally less pathogenic.[80]

In addition, *K pneumoniae* has lipopolysaccharides (endotoxin) covering its outer surface. Upon sensing these lipopolysaccharides, the host organism experiences an inflammatory cascade, contributing to the effects of sepsis and septic shock. The bacterium also forms various fimbrial and non-fimbrial adhesins, allowing it to adhere to host cells and essential to the infectious process.[80] A research report in 2018, noted that siderophores represent another critical virulence factor that enables the bacterium to obtain iron from the host, thus facilitating its dissemination.[81]

There are host variables that increases the risk of infection and colonization. These are; Admission to a ward or healthcare facility, protracted/ usage of intrusive

devices, shabby infection prevention methods, people with alcohol consumption disorder, long-term consumption of broad-spectrum antibiotics, taking corticosteroids and the immunocompromised with conditions such as chronic obstructive pulmonary disease (COPD), peripheral vascular disease, kidney disease or bile disease, diabetic and cancer patients. Bacteria can infect a host directly or indirectly through an aspirated oropharynx and the symptoms and course of treatment can be determined depending on where the infection is located.

2.3.2 Epidermiology

K pneumoniae mainly inhabits humans 5% to 38% of individuals in the general population carrying the organism in their feces and 1% to 6% in their nasopharynx. The patient's digestive system and the hands of hospital staff are the primary sources of infection[82] which can result in nosocomial epidemics. However, individuals of Chinese ancestry and those with persistent alcoholism are more likely to be colonized by *K pneumoniae*. Hospitalized patients have higher carrier rates than the general population, with up to 77% of patients' feces showing colonization rates associated with the number of antibiotics administered.[83]

Infections caused by *K pneumoniae* are considered an endemic opportunistic pathogen that imposes a substantial burden on healthcare in all affected body locations.

2.3.3. Klebsiella pneumoniae Associated Diseases

2.3.3.1 Klebsiella pneumonia

The most frequent illness brought on by Klebsiella bacteria outside of a hospital is pneumonia, most frequently seen as bronchopneumonia and bronchitis. These individuals are more likely to experience pleural adhesions, lung abscess, cavitation and empyema. Even with antibiotic treatment, it has a fatality rate of about 50%.

K pneumoniae can cause two types of pneumonia: community-acquired pneumonia and hospital-acquired pneumonia. While relatively uncommon, community-acquired pneumonia is still a relatively frequent diagnosis, with *K pneumoniae* responsible for approximately 3% to 5% of these cases in the west while they can account for 15% of pneumonia infections in underdeveloped nations like Africa.

K pneumoniae is a significant cause of hospital-acquired pneumonia globally, accounting for approximately 11.8% of cases.[84] *K pneumoniae* is the leading cause of ventilator-associated pneumonia, accounting for 8% to 12% of cases, whereas it only accounts for 7% of pneumonia cases in non-hospitalized individuals.[85-86] Individuals with alcoholism and septicemia have a mortality rate ranging from 50% to 100% when infected with *K pneumoniae*. Moreover, *K pneumoniae* is now recognized as the most frequent cause of hospital-acquired pneumonia in the United States.[77] Patients with COPD, hospital-acquired urinary tract infections, and those who aspirate are also at risk.

The host's defense against *K pneumoniae* invasion relies on two crucial factors: polymorphonuclear granulocytes that phagocytose the bacteria and serum complement proteins that exhibit bactericidal properties. During *K pneumoniae* infection, the alternative complement activation pathway is known to be more active. Studies have shown that lipopolysaccharide-binding protein and neutrophil myeloperoxidase play a crucial role in defense against *K pneumoniae* pathogenesis. Elastase's oxidative inactivation is also involved, and LBP facilitates the transfer of bacteria's cell wall components to the cells. Common symptoms of *K pneumoniae* infection include fever, nausea, tachycardia, vomiting, and coughing up a distinctive sputum. Individuals with underlying health conditions such as alcoholism are more susceptible to *K pneumoniae* infection.

2.3.3.2 Hypervirulent Klebsiella pneumonia

A novel strain of *K pneumoniae* known as hypervirulent (HVKP) is significantly more virulent than the typical *K pneumoniae* (cKp). While cKp is an opportunistic pathogen that usually causes nosocomial infections in immunocompromised patients,[87] HVKP is a greater clinical concern as it can infect almost any part of the body and can even affect healthy individuals in the community. This pathotype is characterized by a large virulence plasmid and potentially other conjugative elements that contain the genetic components responsible for its heightened virulence.

Initially observed in the Asian Pacific Rim with high mortality rates, hypervirulent Klebsiella pneumoniae (HVKP) has now become a global phenomenon.[88-89] Unlike the original cKp, which mainly affects immunocompromised patients in healthcare facilities, HVKP poses a greater threat as it can infect healthy

individuals in the community and cause infections in almost any part of the body, including endophthalmitis, necrotizing fasciitis, pneumonia, and meningitis. When highly drug-resistant cKp strains acquire virulence traits unique to HVKP, it leads to the emergence of novel HVKP strains causing nosocomial infections. The hypermucoviscous phenotype is a visual characteristic of these strains, and a string test can aid in the diagnosis. However, there are currently no universal guidelines for diagnosis and treatment, and further tests and treatments are decided on a case-by-case basis.

These recently discovered strains were reported as overproducing siderophores for iron uptake and other capsule components. Although early research indicated that HVKP is rather responsive to antibiotic therapy, it has subsequently been demonstrated that such strains can pick up resistance plasmids and develop multiple resistances to different antibiotics.

To contract *K pneumoniae*, a person must come into contact with the bacterium, either in the bloodstream or the respiratory system. In healthcare settings, the transmission of *K pneumoniae* can occur through direct contact with infected patients or contaminated surfaces, such as the hands of medical staff or other patients. Although the role of environmental transmission remains uncertain and requires further research, *K pneumoniae* does not spread through the air. Patients on ventilators, with intravenous catheters, or open wounds are at an increased risk of exposure to *K pneumoniae* in medical settings. Medical equipment and procedures also pose a risk for *K pneumoniae* entry into the body and subsequent infection.

K pneumoniae is the second most prevalent gram-negative bacterium responsible for causing bloodstream infections (BSI), following *E coli*.[77] While liver disease and diabetes mellitus have been strongly associated with community-acquired (CA) *K pneumoniae* BSI, cancer is the primary underlying condition linked to BSI acquired in hospitals.[90] BSI may result from an initial infection without a known cause. It is worth noting that BSI often occurs as a secondary infection that spreads into the bloodstream from an identified source. The urinary system, gastrointestinal tract, intravenous or urinary catheters, and pulmonary sites are common sources of secondary BSI. *K pneumoniae*-induced bloodstream infections (BSI) have a case fatality rate ranging from 20-30%, and the estimated population mortality rate is 1.3 per 100,000 individuals.[91]

2.3.3.3 Urinary Tract Infection: *K pneumoniae* has been identified as a cause of catheter-associated UTIs (CAUTIs) when it enters the urinary tract. Klebsiella has the ability to adhere to catheters and form biofilms which is believed to facilitate infections.[92] In addition, Klebsiella is responsible for infections at surgical sites and wounds, accounting for about 13% of all Klebsiella infections.[77] Individuals who have long-term urinary catheterization, which involves inserting a tube into the body to drain and collect urine from the bladder, or kidney disease[93] and those with a uterus are at an increased risk of developing these infections, although they can affect anyone.[94]

2.3.3.3.1 Symptoms Include:

- Urge to urinate often, burning and discomfort during urination, bloody or murky urine.
- Passing tiny quantities of urine, back or pelvic pain, lower abdominal discomfort and fever. Chills, dizziness, nausea and side and upper back discomfort.
- Those who get an upper or lower UTI. Both have comparable symptoms but upper UTIs are more severe than lower UTIs and may involve more systemic symptoms.
- The majority of UTI sufferers will exhibit symptoms. Patients who have comparable symptoms most likely don't have a UTI but their urine test results are abnormal and suggest that they do.

2.3.3.4 Skin Infection or Soft Tissues: *K pneumoniae* can enter the body through a skin break and cause infections in the skin or soft tissues, often resulting from surgical wounds or traumatic injuries. These infections can lead to various illnesses such as myositis, necrotizing fasciitis, and cellulitis. Symptoms may include fever, redness, swelling, discomfort, flu-like symptoms, exhaustion, as well as wounds or ulcers that may develop on the lining of the stomach, small intestine, or esophagus, depending on the type of infection.

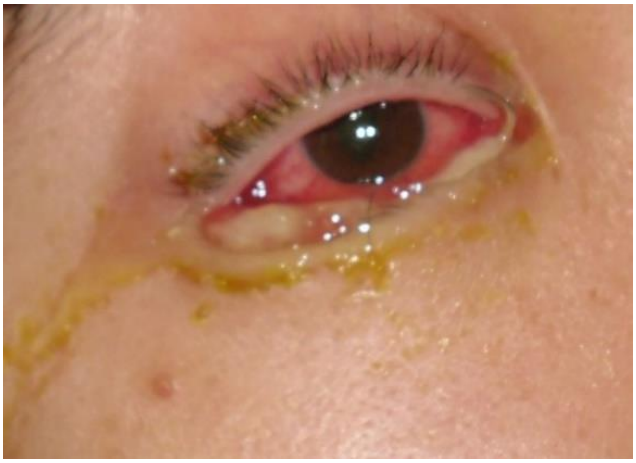
2.3.3.5 Meningitis: Although rare, *K pneumoniae* can cause bacterial meningitis, which is characterized by inflammation of the membranes surrounding the brain and spinal cord. This happens when the bacteria invade the fluid around these structures. Most cases of *K pneumoniae* meningitis occur in medical facilities.[95] Symptoms of meningitis usually appear abruptly and include a high fever, headache, and a stiff neck.

Other signs may include nausea, vomiting, sensitivity to light (photophobia), confusion, and in rare cases, seizures.

2.3.3.6 Endophthalmitis: *K pneumoniae* can spread to your eyes and cause endophthalmitis if it is present in your blood. It is an infection that can make the white of your eye swell and eventually cause blindness. In Western nations, this kind of endophthalmitis is uncommon.[96] Eye discomfort, redness, white or yellow discharge, white cloudiness on the cornea, photophobia, and impaired vision are possible symptoms.

Figure 4

A previously healthy 33 year old Chinese male presented with endophthalmitis.[97]



2.2.3.7 Abscess with Pyrogenic Liver: In the United States, more persons have experienced a pyogenic liver abscess as a result of *K pneumoniae* in recent years.[98] People who have diabetes, an alcohol use disorder or who have been taking antibiotics for a long time are more likely to develop *K pneumoniae* liver abscesses.[99] Frequent signs and symptoms include: Fever, upper right abdominal discomfort, nausea, vomiting and diarrhea with blood contamination.

When *K pneumoniae* enters your body, it can cause bacteremia or the presence of germs in your blood. Primary bacteremia occurs when *K pneumonia* directly invades your circulation. Secondary bacteremia occurs when *K pneumoniae* spreads to your blood from an infection in another part of your body. A study conducted in 2016 found that approximately 50% of blood infections caused by Klebsiella bacteria

originate from infections in the lungs.[100] Symptoms of bacteremia often occur suddenly and may include shaking, chills, or fever. Prompt treatment for bacteremia is necessary as it can progress to sepsis, a severe reaction of the body to an infection, which can be life-threatening if left untreated.

Middle-aged and older males are more likely to have crippling illnesses than women. This patient group, which includes people with diabetes, alcoholism, cancer, liver illness, chronic obstructive lung disorders, glucocorticoid medication, renal failure, and some occupational exposures, is thought to have weakened respiratory host defenses (such as paper mill workers). Many of these illnesses (nosocomial infections) are acquired when a person is in the hospital for another cause.

In addition to pneumonia, Klebsiella can also infect the lower biliary system. Pneumonia, thrombophlebitis, cholecystitis, diarrhea, upper respiratory infection, osteomyelitis and sepsis are among the list of clinical disorders. The danger of device contamination increases for patients who have invasive devices in their bodies including those used in newborn wards, respiratory support devices and urine catheters.[101] The likelihood of nosocomial infection with Klebsiella bacteria can also be influenced by the use of antibiotics. When germs enter the bloodstream, sepsis and septic shock may occur.

Elderly adults with urinary tract infections, Klebsiella comes in second place to *E coli*. Also, it is an opportunistic infection for those who have intestinal pathogenicity, rhinoscleroma, nasal mucosa atrophy, and chronic pulmonary illness. *K pneumoniae* is developing new strains that are resistant to antibiotics.

2.4 Proteus Mirabilis

In 1885, Gustav Hauser, a German pathologist, first discovered a microorganism with an exceptional ability to evade the host's immune system.[102] Hauser named this species Proteus after the Greek god who could change his shape. The Proteus genus comprises Gram-negative, rod-shaped bacteria belonging to the Enterobacteriaceae family.[103] Proteus mirabilis is a gray, smooth, domed-shaped, facultatively anaerobic, gram-negative rod with rounded edges that exhibits urease activity and swarming motility. *P mirabilis* is commonly found in the environment, such as soil, water, and the gastrointestinal tracts of animals and humans.[104] It is known for its swarming ability over agar surfaces and its capability to outcompete other microorganisms, making it a notable bacterium in clinical laboratories and

microbiology survey courses. It is a lactose-negative, indole-negative, hydrogen sulfide-producing, motile, and urease-positive Gram-negative rod.[105]

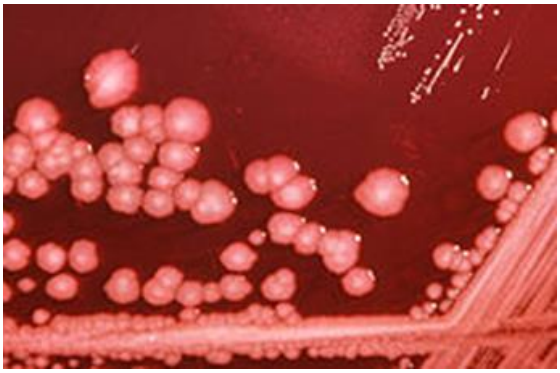
In healthy subjects, it is an opportunistic pathogen that makes up less than 0.005% of the human gastrointestinal microflora.[106] Although normally not harmful but can cause problems when it comes into touch with urea in the urinary tract. Infection may then spread to different body parts from there. *P mirabilis* is responsible for about 90% of all Proteus infections in people which are considered community acquired infection[107-109] Patients with a history of recurrent infections, structural abnormalities in their urinary system, urethral instrumentation, hospitalization, and co-infection with organisms such as Klebsiella, Enterobacter, Pseudomonas, Staphylococci, and Enterococci are more susceptible to Proteus infections.[110]

One distinguishing characteristic of *P mirabilis* as first described by Hauser in 1885, is its capacity to transform from short vegetative swimmer cells to an elongated and highly flagellated when found in swarmer forms[111] Its genome contains the genetic instructions for at least 10 adhesion molecules, making it incredibly sticky and mobile motile thanks to adhesion and swarming growth elements. This causes it to thrive easily by evading the host's immune system and avoiding capture. It also forms a concentric rings during its swarming movement on a blood agar plate thereby making it simple to identify.

P mirabilis can be detected in cases of asymptomatic bacteriuria, particularly in the elderly and individuals with type 2 diabetes, and can cause symptomatic urinary tract infections such as cystitis and pyelonephritis.[112-113] These infections can progress to bacteremia, leading to life-threatening urosepsis. Furthermore, *P mirabilis* infections can also result in the development of urinary stones (urolithiasis).

Figure 5

Colonies of Proteus mirabilis bacteria grown on a xylose-lysine-deoxycholate (XLD) agar plate.[114]



Although it is debatable whether *P mirabilis* is a pathogen, a temporary organism or a commensal, it is frequently isolated from the digestive tract[115] It was also reported in a research, that the majority of urinary tract infections (UTIs) caused by *P mirabilis* result from bacterial migration from the gastrointestinal tract to the catheter lumen or from contaminated urine along the catheter's mucosal sheath.[116]

2.4.1 Virulence Factors

Proteus species have been found to be capable of spreading infections, particularly in hospital settings. The transmission of these illnesses is likely to occur through person-to-person contact, where the skin or oral mucosa of patients and staff members become colonized. Despite not being a common cause of nosocomial infections, there have been documented cases of Proteus species causing infections in healthcare facilitie.[105,117] Some evidence suggests that certain patients with Proteus mirabilis urinary tract infections may have the same strain of bacteria in their feces, while others do not.[118]

2.4.2 Urease

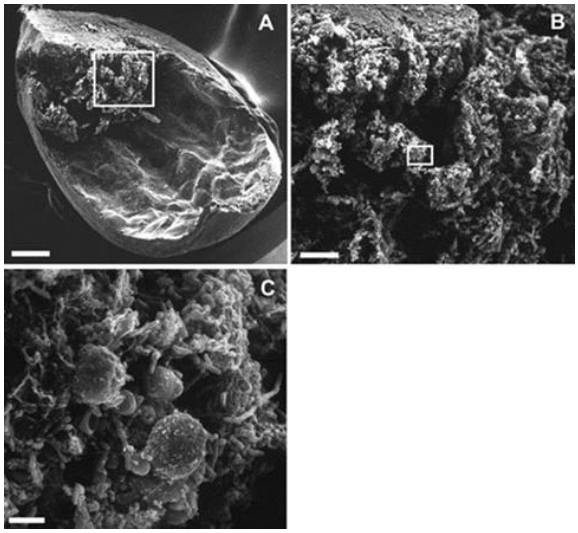
Normally, urine has a neutral or slightly acidic pH. However, when a patient wears a catheter for an extended period, crystalline deposits from the urine can form a crust around the catheter, obstructing the flow of urine through the urethra. The encrusted crystals on the catheter provide an opportunity for *P mirabilis* to colonize in large numbers and hydrolyze urea, which increases the environmental pH through the production of ammonia.[119]

Hydrolysis of urea by urease results in the production of ammonia and carbon dioxide. Many types of bacteria prefer ammonia as a nitrogen source, which can be incorporated into biomolecules. Urease activity causes an increase in local pH due to the release of ammonia. In the urinary tract, this alkaline pH can lead to the formation of urinary stones composed of calcium phosphate (apatite) and magnesium ammonium phosphate (struvite), as well as the precipitation of calcium and magnesium ions.[120] It majorly causes the formation of urinary stones, which mediates pathogenicity. These stones can harm tissue, obstruct urine flow and grow quite large >1 cm^2.[121-122] Similar crystals have been observed in urinary epithelial cells cultured in a laboratory that have been infected with invasive *P mirabilis*.[123]

Although other bacterial species that produce urease are associated with catheter-associated UTIs, only *P mirabilis* has been positively correlated with catheter obstruction. Urinary stones can become colonized by bacteria, providing a protective environment that shields pathogens from antibiotics and the immune system.[124] This can make urinary stones a focal point for other bacterial species to cause UTIs.

Figure 6

The presence of P mirabilis in a bladder stone induced by urease can be observed in the following images: A) A quarter section of the bladder of an experimentally infected mouse (500 µm scale bar). B) A higher magnification of the area highlighted in panel A (100 µm scale bar). C) A further magnified view of the region indicated in panel B, revealing individual bacteria (5µm scale bar).[124]



2.4.3 Flagella and Swarming Motility

Multicellular, flagellated bacteria can engage in a specialized type of movement called swarming, which aids in the spread of their populations to new areas Howery KE, et al. (2015). In the case of *P mirabilis*, this ability is crucial to its pathogenesis, as it is linked to the bacteria's capacity to produce virulence proteins.[111]

In liquid culture, *P mirabilis* appears as a vegetative cell that measures approximately 2µm in length and is equipped with 4-10 peritrichous flagella that it uses for forward movement. Swarming cells, on the other hand, only emerge when the bacteria is grown on solid surfaces, necessitating the capacity to identify such surfaces. *P mirabilis* detects solid surfaces by inhibiting the rotation of its flagella, which alerts the bacteria to its presence. Upon contact with a solid surface and the satisfaction of other conditions, *P mirabilis* differentiates into a swarmer cell.

This differentiation process involves multinucleation, a more than 50-fold increase in the number of flagella on the cell surface, and elongation of the cell, which can be up to 50 times longer than the vegetative cell.[125] As the bacteria responds to external stimuli, the swarming process continues in cyclical populations that migrate, consolidate, and differentiate.

On solid growth media, this cycle is repeated as *P mirabilis* forms transparent coatings and releases hydrogen sulfide gas. The bacteria is characterized by its peritrichous flagella, which enable a cooperative group motility that allows organisms to move across the surface of solid media or objects, preventing the growth of unrelated strains. When two swarming strains overlap, a macroscopically discernible line of diminished bacterial growth appears, exhibiting a highly distinctive bulls-eye pattern due to the cells cycling between the vegetative and swarming states.[126] This phenomenon, known as the Dienes line, is named after its discoverer Louis Dienes in 1946.[127]

P mirabilis is most frequently found in the urinary system, particularly in severe or catheter-related infections. It has the ability to swarm across silicone or latex catheters, making it particularly relevant for catheterized patients.[128-129] As several virulence factors are expressed more frequently during swarming, *P mirabilis* colonizing catheters may already be primed to infect the urinary tract. The unique bulls-eye pattern allows for *P mirabilis* to be distinguished from other swarming bacterial species, with each ring developing as the bacteria enter their consolidation stage and their population grows.[111]

Figure 7

Proteus mirabilis swarming phenomenon having peritrichous flagella and motility.[130]

2.4.4 Biofilm Formation

P mirabilis employs a wide range of virulence factors to initiate catheter-associated urinary tract infections (CAUTIs). Certain virulence characteristics, including swarming motility, fimbriae, urease production, capsule polysaccharide, and efflux pumps, have been associated with their ability to form biofilms.[131]

The exceptional swarming capabilities of *P mirabilis* are widely recognized. When an organism grows on solid surfaces, the short, rod-shaped "swimmer cells" begin to differentiate into very elongated, hyper-flagellated "swarmer cells," which can arrange themselves into multicellular rafts. These cell rafts can move swiftly and cooperatively over solid surfaces.[132] Hence, the swarming motility of *P mirabilis* may facilitate its migration from the periurethral region along the catheter surface to the urinary bladder, thereby leading to CAUTIs.[133] Inability of *P mirabilis* to migrate along the surfaces of catheters has been associated with loss of the swarming capacity brought on by mutations.[128]

Furthermore, swarmer cells often display heightened expression of virulence factors, enhancing their ability to adhere to catheter surfaces and bladder epithelium Fraser et al. (2002). Nonetheless, certain studies have revealed that *P mirabilis* requires suppression of swarming to attach to catheter surfaces and initiate biofilm formation.[133,135] The initial stage of catheter surface biofilm formation involves the attachment of fimbriae (adhesins) either to the protein coat derived from bodily fluids or directly to the catheter material.[136-137]

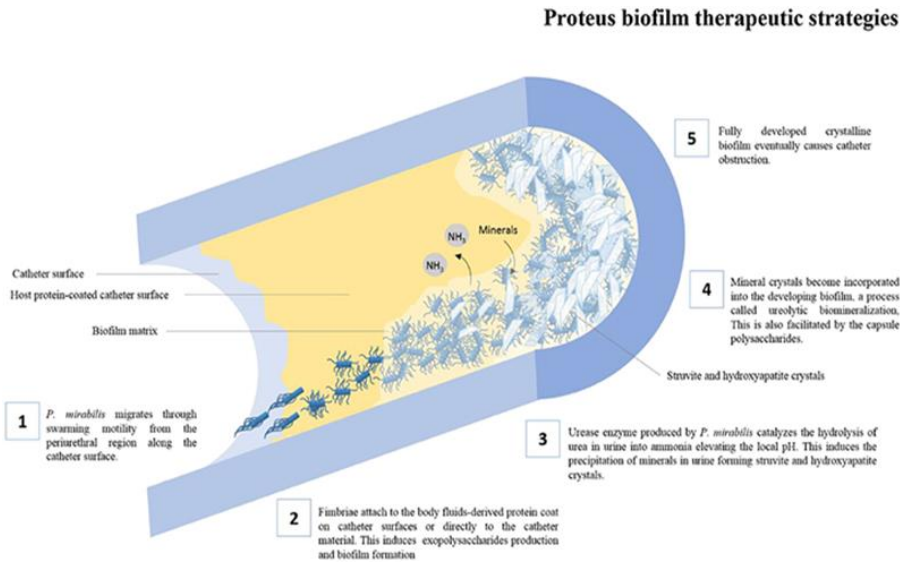
One of the distinguishing features of *P mirabilis* is its ability to form distinctive crystalline biofilms that frequently lead to catheter encrustation and blockage, further complicating CAUTIs. Urease enzyme and capsule polysaccharides as two components of *P mirabilis* pathogenicity that play a role in the development of crystalline biofilms (CPSs).[138] The vast majority of clinical strains of *P mirabilis* are capable of producing an extremely potent urease enzyme, which can elevate the local urinary pH by breaking down urea in urine into ammonia. When there is local supersaturation and precipitation of minerals commonly present in urine, such as calcium phosphate, it usually results in the formation of struvite crystals (ammonium magnesium phosphate) and hydroxyapatite crystals.[139] These crystals are incorporated into the developing biofilm via a process known as Ureolytic biomineralization,[138] which involves the absorption of crystals produced during the breakdown of urea in urine. The production of a large amount of highly alkaline ammonia by the urease

enzyme can cause direct harm to mammalian cells, resulting in tissue damage, and is also a significant contributor to the development of crystalline biofilms.[140]

Aside from *P mirabilis*' ability to break down urea, it has also been found that its CPSs accelerate the process of mineral crystal formation.[138] This is due to the acidic composition of bacterial CPSs, which gives them a strong attraction to electrostatically bind with metal cations found in urine.

Figure 8

Illustration of various virulence factors that contribute to formation of P mirabilis biofilms. This depicts the contribution of different virulence factors to the creation of crystalline biofilms by P mirabilis on catheter surfaces.[141]



2.4.5 Fibriae and Adenesin

Bacterial fimbriae, also known as pili, are hair-like protein structures that protrude from the bacterial surface and aid in adhesion to surfaces. Gram-negative bacteria produce a subset of chaperone-usher fimbriae for secretion and assembly.[142] Although the exact functions of most of these fimbriae remain unclear, all 17 operons have been shown to be transcribed, with *P mirabilis* encoding the majority of them. [143] PCR tests have revealed that at least 14 distinct fimbriae are encoded by 85% of clinical isolates[143] and transmission electron microscopy has revealed that *P mirabilis* can develop multiple fimbrial morphologies simultaneously, unlike other bacteria such as *E coli*.[144] *P mirabilis* dedicates a larger portion of its chromosome to encoding fimbriae than uropathogenic *E coli*, which typically encodes 9-12 fimbrial operons.[145]

Studies have shown that *P mirabilis* -encoded fimbriae play a role in urinary tract infections (UTIs), as is often the case with fimbriae in other pathogens.[146-148] *P*

mirabilis can adhere to human uroepithelial cells, regardless of the bacterial source, which is consistent with the conservation of fimbrial genes in this species.[143] Although mutations in fimbrial genes do not prevent bacteria from colonizing the urinary tract, they do reduce their ability to compete and challenge in direct competition studies, suggesting redundancy or overlapping functions among the 17 fimbriae.[149] *P mirabilis* fimbriae have also been evaluated as potential vaccine candidates due to their surface localization, abundance, and immunogenicity, with moderate success.[150-153]

2.4.6 Toxins

Several putative toxins have been identified in some strains of *P mirabilis* as potential virulence factors. Among them, Proteus toxic agglutinin, metalloprotease, and hemolysin have been thoroughly characterized. Hemolysins are a type of pore-forming toxin frequently produced by pathogenic bacteria that are released by the hemolysin enzyme. These toxins enter eukaryotic cell membranes, causing sodium ions to leak out and damage the cell. Proteus species have been found to possess two hemolysins, one calcium-dependent and similar to the β-hemolysin of *E coli* (hlyA), and the other calcium-independent.

HpmA is the primary hemolysin in *P mirabilis* and appears to be the only hemolysin encoded by the species. It is present in a high percentage of clinical and fecal isolates of *P mirabilis* from Brazil and the US.[154] HpmA is responsible for cytotoxicity to human renal proximal tubular epithelial cells and can mediate lysis of various cell types from different host species, including HRPTECs. HRPTECs act as a barrier of defense for the kidney parenchyma. The involvement of HpmA may be crucial in facilitating the dissemination of *P mirabilis* to the kidneys and triggering the onset of pyelonephritis.[155]

2.4.7 Proteus Mirabilis Associated Diseases

2.4.7.1 Urinary Tract Infection and Catheter Associated Urinary Tract Infection

P mirabilis is a frequent cause of both community-acquired and catheter-associated UTIs in individuals with structural or functional urinary tract abnormalities.[156] This poses a significant challenge for patients who require long-term indwelling urinary catheterization since they are at a heightened risk of developing UTIs from the catheter, which can lead to encrusted and obstructed catheters and make

infections more difficult to treat.[158] Patients may experience painful bladder distension, pyelonephritis, urine retention, and reflux as a result of these infections, which can result in severe and potentially life-threatening conditions such as septicemia and endotoxic shock.[158] Furthermore, when the catheter is removed, it could harm the mucosa of the bladder and urethra[159] necessitating the replacement of clogged catheters to avoid CAUTIs, which results in more nursing visits and emergency referrals.

The formation of drug-resistant crystalline biofilms has been linked to *P mirabilis* persistence in the urinary system, which evades the human immune response.[160] *P mirabilis* colonization of the intestinal tract serves as a source for sporadic colonization of the periurethral area. Upon catheter insertion, the organism contaminates the urinary catheter and is then transported to the bladder.[118] Exopolysaccharides are produced when a catheter or bladder epithelium is adhered to urinary bladder, leading to biofilm formation.[161]

The incidence of *P mirabilis*-caused UTIs varies between 1% and 10% depending on the study's geographic setting, the kinds of samples used to gather data, and the patient characteristics studied. *P mirabilis* is responsible for 4% of almost 3,000 UTI cases in the most recent significant North American investigation.[162] In 2006, UTIs cost the American healthcare system $3.5 billion and resulted in 11 million doctor visits[163] *P mirabilis* is a significant contributor to catheter-associated UTI (CAUTI), causing 10-44% of long-term CAUTIs and costing $43-256 million in the US annually.[160,164-165] The incidence of *P mirabilis* infections is higher in severe cases of urinary tract infections, particularly in patients with spinal cord damage or anatomical abnormalities.

Elderly individuals experience the highest prevalence of *P mirabilis* CAUTI, while receiving long-term catheterization. Recent studies have reported that *P mirabilis* is present in 5-20% of cases of Gram-negative bacteremia, particularly in individuals with concomitant UTI. Geriatric patients with *P mirabilis* bacteremia have been reported to have a mortality rate as high as 50%.[166-169]

Apart from urinary tract infections, *P mirabilis* has been associated with various other infections such as respiratory tract infections, chronic suppurative otitis media, endophthalmitis (infection of the inner part of the eye), ear infections, nose infections, skin infections, throat infections, cystitis, pyelonephritis, prostatitis, burns,

and wounds. It has also been linked to neonatal meningoencephalitis and meningitis.[160,170]

It is also a common cause of bacteremia following catheter-associated UTI [171] and in rare cases has been reported to cause cellulitis, endocarditits, mastoiditis, empyema, and osteomyelitis.[170] It has also been suggested that *P mirabilis* could have a role in the etiology of rheumatoid arthritis.[172] Several studies have shown a connection between *P mirabilis* and rheumatoid arthritis, whereas others have not. It is hypothesized that antibodies to the enzymes hemolysin and urease can then detect self-antigens in rheumatoid arthritis patients.[173]

2.5 Antibiotic Resistance

The development of antibiotics is one of the most remarkable accomplishments of modern medicine and has undoubtedly saved countless lives. Antibiotics have been critical in managing common, serious, and life-threatening infections, as well as in preventing complications.[174] Over the last 75 years, more than 150 antibiotics have been identified since the discovery of penicillin [175] The emergence of antibiotic resistance due to inappropriate use and misuse of antibiotics has become a significant threat to public health and the effectiveness of antibiotics.

The extensive use of β-lactam antibiotics has contributed to the emergence of resistant Enterobacteriaceae. The production of extended-spectrum β-lactamases (ESBL) is the primary mechanism of β-lactam resistance, which has led to a global increase in the prevalence[176-177] of resistance among Enterobacteriaceae species such as *E coli*, Klebsiella spp., Enterobacter spp., Proteus spp., Citrobacter spp., Morganella spp., Salmonella spp., and Serratia spp.[178] which are the leading causes of hospital and community-acquired infections.[179-180]

Gram-negative bacteria develop ESBL enzymes as a means of resistance against extended-spectrum penicillin, cephalosporins, and monobactams, with the exception of cephamycins and carbapenems. Clavulanic acid, however, can inhibit the β-lactamase enzyme.[177,179,181] The spread of this resistance affects β-lactams and other commonly used antibiotics such as fluoroquinolones, aminoglycosides, and sulphonamides[182-183] leading to the dissemination of multidrug-resistant (MDR) bacterial strains.[184] As a result, morbidity and mortality rates have risen, therapeutic options are limited, and treatment costs are high.[11]

β-lactamase and ESBL genes are frequently carried on highly mobile plasmids that frequently also harbor resistance genes to other antimicrobial classes[185] Infections can spread between and within hospitals, as well as between the general public and healthcare facilities, thanks to ineffective infection prevention and control procedures.[186-190] Currently, more than 200 distinct ESBLs have been described in different regions.[17,179] There have been widespread reports of outbreaks involving these resistant pathogens in members of the Enterobacteriaceae and Pseudomonas spp., which has limited the range of available therapeutic options. ESBL-producing bacteria are probably more common than is currently believed because they frequently go unnoticed by standard susceptibility testing procedures.[191]

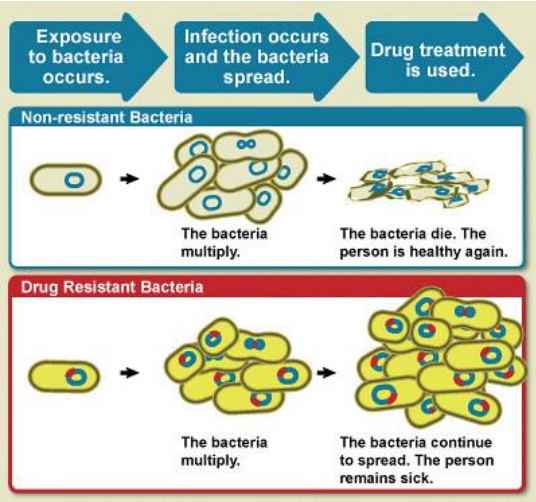
ESBLs can be classified into three main categories: TEM, SHV, and CTX-M. While *E coli* and *K pneumoniae* are the most common ESBL-producing pathogens globally, other members of the Enterobacteriaceae family and non-fermenters have also been found to produce these enzymes.[192]

Antibiotic resistance is a major concern in hospital settings, where patients may be exposed to antibiotics and come into contact with the bacterial flora of other patients if infection control measures are not followed. Antibiotic-resistant bacteria can spread to other patients, and the problem can worsen if these resistant species transfer antibiotic resistance genes to other bacteria.[193]

Antibiotic resistance can be inherent or acquired. Inherent resistance means that the drug cannot affect "wild-type" bacteria that have not been previously exposed to it. For instance, vancomycin is not effective against gram-negative bacteria. Acquired resistance can result from mutation or acquisition of new genetic material from other bacteria. Mutations can prevent antibiotics from affecting the bacterial target, while the acquisition of genes that encode for β-lactamase production can lead to resistance to antibiotics like Ampicillin by *E coli*. For example, *E coli* may be susceptible to both Ampicillin and Ciprofloxacin but mutation of its genetic material can lead to Ciprofloxacin resistance.[194-195]

Figure 9:

Distinction between bacteria that are drug resistant and non- drug resistant bacteria.[196] When non-resistant bacteria are treated with drugs, they die. Drug-resistant bacteria proliferate even after drug therapy and the bacteria continue to spread.



One of the six drug-resistant microorganisms for which new treatments are urgently required is Klebsiella spp. and *E coli*, according to a recent research from the Infectious Diseases Society of America (IDSA) due to the community's increasing importance of *E coli* producing ESBL multi drug resistant bacteria.[197]

Unfortunately, resistance to a particular class of antibiotics may develop as a result of numerous mechanisms of resistance co-operating. Any β-lactam antibiotic enters the bacterial cell through the outer membrane proteins, which serve as the antibiotics' entry points. These proteins might be lost which would lower the antibiotic's absorption and antimicrobial activity. In cases where there is a high inoculum of organisms, the extensive levels of β-lactamase synthesis may surpass the effects of β-lactamase inhibitors at certain infection sites, particularly those with a high organism load, such as intra-abdominal abscesses or severe cases of ventilator-associated pneumonia.[198]

2.6 Quinolone Resistance

The synthetic antibacterial agent class known as quinolones was first developed during the period spanning from the late 1980s to the early 1990s. As a result of its effectiveness, broad spectrum of action, excellent oral absorption, and nearly absence of side effects, they have been used extensively as treatments in both human and veterinary medicine.[199-200] Quinolones are the preferred antibiotic since they are bactericidal to some Gram positive and Gram negative bacteria.[201] Their primary and secondary targets of DNA gyrase and topoisomerase IV respectively, during the growth and reproduction stages, the quinolone antibiotics interrupt DNA replication.[202] Initially, resistance to quinolones was considered rare due to their

remarkable in-vitro effectiveness. However, with the introduction of these drugs, there has been a rise in the prevalence of resistant strains of Gram-negative bacteria, including *E coli.*[203]

The utilization of quinolones in veterinary and animal medicine has experienced a substantial increase due to their selective inhibitory actions against pathogenic bacterial strains, which account for over 20% of the world's antibiotic consumption.[204] Over the past three decades, there has been a sharp increase in the prevalence of quinolone resistance, primarily as a result of several bacterial strains acquiring plasmid-mediated resistance mechanisms.[205-206]

Bacteria have developed various mechanisms to counteract the impact of quinolones in their environment. These include overexpression of proteins needed for quinolone efflux pumps and uptake systems, changes in determinants that encode quinolone enzyme targets, and possession of plasmid-mediated quinolone resistance (PMQR) genes.[207-208] In addition to the original discovery of the plasmid-mediated resistance gene qnrA1 in a clinical isolate of *K pneumoniae*,[199-200] subsequent research has identified more quinolone transferable resistance plasmids,[208-209] as well as other resistance elements, such as efflux pumps.[207,210]

The global prevalence of quinolone resistance on Enterobacteriaceae that produce extended spectrum β-lactamases (ESBL) has increased immersely.[211] The primary cause of quinolone resistance is chromosome mutations that occur in the quinolone resistance-determining region of the DNA gyrase (gyrA and gyrB) and topoisomerase IV (parC and parE) genes.[212] Plasmid-mediated quinolone resistance (PMQR) determinants have been identified, with the qnr protein from the pentapeptide repeat family being the first to be discovered in a strain of *K pneumoniae* in the United States.[213]

Topoisomerase and DNA gyrase are in contact with Qnr. To avoid quinolone inhibition, IV. In the years that followed, the plasmid-mediated qnr determinants qnrB, qnrC, qnrD, and qnrS, which are all distantly related, were reported in Enterobacteriaceae. Since the qnr genes are frequently plasmid-integrated, they are especially vulnerable to interspecies transfer.[207]

Moreover, plasmids that carry quinolone resistance genes often harbor other antibiotic resistance genes, such as extended-spectrum beta-lactamases (ESBLs), which promote the spread and selection of fluoroquinolone-resistant strains in response to unrelated drug classes, and vice versa.[214] PMQR comprises of the

quinolone resistance (Qnr) proteins (qnrA, qnrB, C, D, and QnrS). These guard against quinolone inhibition of DNA gyrase and topoisomerase IV, and aac (6′)-Ib-cr (aminoglycoside acetyltransferase variant), which acetylates aminoglycoside, ciprofloxacin. Additionally, the plasmid-mediated efflux pumps oqxAB and qepA.[207] Although the PMQR determinants promote chromosome-encoded quinolone resistance, they also cause low-level quinolone resistance.[215] Multidrug-resistant (MDR) ESBL-producing Enterobacteriaceae have been found to be particularly resistant to aminoglycosides, fluoroquinolones, and trimethoprim/sulfamethoxazole.[216]

The ESBL genes and PMQR genes are frequently found on the same plasmid.[217] In order to spread PMQR determinants among various Enterobacteraceae species, conjugation can transfer resistance plasmids with genes encoding ESBLs.[218] The simultaneous presence of ESBLs and PMQR genes poses a significant challenge due to the development of multidrug-resistant (MDR) strains.

2.7 History

The importance of quinolones as a therapy for various clinical symptoms was discovered in 1962. The first was nalidixic acid, which George Lesher of the Sterling-Winthrop Research Institute created synthetically. Years ago, it was created as a byproduct of the manufacture of chloroquine from the separation of chloro-1-ethyl-1,4-dihydro-4-oxo-3-quinoline carboxylic acid.[219] The origin of quinolone drugs can be traced back to the antimalarial drug chloroquine, and it took several years after its invention for nalidixic acid to be approved for the treatment of urinary tract infections caused by Gram negative bacteria. In addition to having some cytotoxic effects on the digestive tract and the central nervous system, this substance does not have a significant impact on Gram-positive bacteria. The first generation of quinolones are characterized by their impact on Gram-negative bacteria.[220]

Table 1

List of common quinolones and fluoroquinolones.[221]

Generic name	Brand names examples
Cinoxacin	Discontinued in the U.S.
Ciprofloxacin	Cipro, Proquin XR

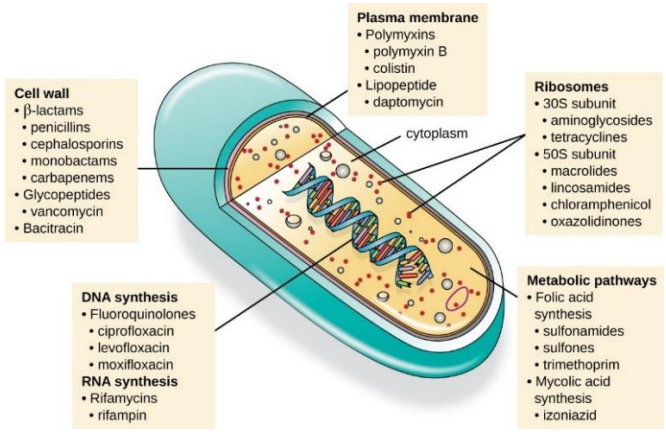
Delafloxacin	Baxdela
Garenoxacin	Geninax
Gatifloxacin	Gatiflo, Tequin and Zymar
Gemifloxacin mesylate	Factive
Levofloxacin	Levaquin
Moxifloxacin	Avelox
Nalidixic acid	Discontinued in the U.S.
Norfloxacin	Discontinued in the U.S.
Ofloxacin	Floxin
Sparfloxacin	Discontinued in the U.S.

Quinolone antibiotics like Ciprofloxacin and Levofloxacin are often quite used. Although Enterobacteriaceae family strains are susceptible to quinolones in vitro, there has been a noticeable rise in the rates of resistance. When compared to organisms of the same species that don't produce ESBLs, quinolone resistance is more likely a result of an ESBL-producing organisms.[222] The cause of these co-resistances are not completely understood. Quinolone resistance caused by a plasmid has been documented and may have a role in specific circumstances.[213] Quinolone resistance is commonly attributed to mutations in the genes coding for DNA gyrase and topoisomerase IV, which are the target enzymes of quinolones. If one or two of the genes producing these enzymes are mutated, resistance increases stepwise. Despite incomplete understanding, it seems that alterations to the outer membrane proteins and active efflux pumps, which expel antibiotics from the bacterial cell, are important mechanisms contributing to bacterial resistance to quinolones.

Quinolone mechanism of action is by Inhibition of nucleic acid synthesis, it functions by attaching to elements necessary for DNA or RNA synthesis, interfering with normal cellular functions and ultimately endangering the bacteria's growth and survival.[223]

Figure 10

Site of action for different classes of antibiotics classified based on the bacterial target.[224]



2.8 Classification of β-Lactamase

Members of this family frequently produce the β-lactamases TEM-3, TEM-4 and SHV-2, which give resistance to extended-spectrum cephalosporins with an increased spectrum of activity.[225] Extended-spectrum β-lactamases (ESBLs), a new class of enzymes discovered in the middle of the 1980s, were discovered for the first time in 1979.[226] The prevalence in the general population varies by nation with about 6% in Germany as an example and France,[227-228] 13% in Saudi Arabia[229] and 63% in Egypt.[230] ESBLs are β-lactamases that break down cephalosporins having an oxyimino side chain from the extended-spectrum class. These cephalosporins include oxyimino-monobactam aztreonam, cefotaxime, ceftriaxone, and ceftazidime. As a result, oxyimino-beta lactams and other related antibiotics are susceptible to multi-resistance conferred by ESBLs. Typically, they are derived from genes for TEM-1, TEM-2, or SHV-1 through mutations that change the amino acid configuration surrounding these β-lactamases' active sites. These enzymes can hydrolyze a broader range of β-lactam antibiotics. Recent reports have described an increasing number of ESBLs that are not TEM or SHV lineages.[213] Plasmids are frequently used to encode the ESBLs. ESBL-producing plasmids frequently carry genes encoding resistance to various drug classes, such as aminoglycosides. There are two system used to categorize ESBLs:

- The Ambler classification which divides the enzymes into four groups (A, B, C, and D) based on molecular structure, is the original system of categorizing β-lactamases. As plasmid-mediated enzymes that hydrolyze Oxyimino-Cephalosporins and Monobactams but not Cephamycins or Carbapenems, ESBLs are Class A β-lactamases. Clavulanate inhibits them in vitro. Different ESBL genotypes exist. The SHV, TEM, and CTX-M kinds are the most prevalent.[232]

- A commonly used taxonomy of β-lactamases was created by (Bush et al. 2010) based on their functional traits and substrate profiles. The enzymes are separated into several categories, including group 1 cephalosporinases which clavulanic acid does not inhibit. The larger group 2 broad spectrum enzymes which clavulanic acid typically inhibits. The ESBLs are represented by the subgroup 2be, which begins with the letter "e" for extended spectrum of activity. The majority of ESBLs belong to group 2be, which hydrolyzes clavulanic acid-inhibited (Ambler classification) monobactams, cephalosproins and penicillins. Although the CTX-M genotype was initially not included in the original classification but it meets the requirements for group 2be enzymes.[233]

2.8.1 Tem β-Lactamases (Class A): The most frequent beta-lactamase found in Gram-negative bacteria is TEM-1. The creation of TEM-1 by *E coli* is the cause of up to 90% of the organism's ampicillin resistance.[234] Additionally accountable for the rising prevalence of ampicillin and penicillin resistance in *H influenzae* and *N gonorrhoeae*. Although *E coli* and *K pneumoniae* have the highest prevalence of TEM-type β-lactamases, these enzymes are increasingly common in other species of Gram-negative bacteria. The oxyimino β-lactam substrates can now be accessed thanks to the configuration change brought on by the amino acid substitutions that cause the extended-spectrum β-lactamase (ESBL) phenotype. It is also typical that opening the active site to beta-lactam substrates increases the enzyme's susceptibility to β-lactamase inhibitors, such as clavulanic acid. The ESBL phenotype is caused by single amino acid changes at positions 104, 164, 238, and 240, while ESBLs with the largest spectrum typically contain several amino acid alterations. 140 TEM-type enzymes have currently been described based on various combinations of modifications. The most prevalent in the United States are TEM-10, TEM-12, and TEM-26.[235-237] The name of the Athenian patient (Temoniera) from whom the isolate was extracted in 1963, inspired the word "TEM."[238]

2.8.2 Shv β-Lactamases (Class A): The initials stand for "sulfhydryl reagent variable"[239] SHV-1 and TEM-1 have a similar overall structure and share 68% of the same amino acids. *K pneumoniae* is home to the SHV-1 β-lactamase, which accounts for up to 20% of the ampicillin resistance in this species that is plasmid-mediated. Additionally, the active site of this family of ESBLs has altered amino acids, most

frequently at positions 238 or 238 and 240. There are reported to be about 60 SHV variants. Among the most prevalent are SHV-5 and SHV-12.[235]

2.8.3 Ctx-M β-Lactamases (Class A): The term "CTX-M" stands for "Cefotaxime-Munich".[240] These enzymes are named for their enhanced effectiveness against cefotaxime compared to other oxyimino-beta-lactam substrates, such as ceftazidime, ceftriaxone, and cefepime. They are occasionally acquired via plasmids carrying beta-lactamase genes that are normally present on the chromosomes of Kluyvera species, which are generally harmless commensal microorganisms. Despite sharing only around 40% identity with the commonly isolated TEM or SHV beta-lactamases, the CTX-M enzymes are not closely related to them. To date, more than 172 CTX-M enzymes have been discovered.[241] Some of these enzymes exhibit greater activity against ceftazidime than cefotaxime, despite their names. While primarily identified in *E coli* strains, they have also been detected in other Enterobacteriaceae species and are the most prevalent ESBL type in various regions of South America. Additionally, they are observed in Eastern Europe; the most common strains are CTX-M-14, CTX-M-3 and CTX-M-2. The most prevalent strain of *E coli* in the UK as of 2006 is CTX-M-15[242] which is also very common in the local population. Recent research has revealed that the β-lactamase CTX-M-15 has transferred onto the genome of *K pneumoniae* ATCC BAA-2146.[243]

2.9 Types of Quinolone Resistance

2.9.1 Target-Mediated Quinolone Resistance

Majority of the time, certain DNA gyrase and/or topoisomerase IV mutations are linked to quinolone resistance. Typically, a single type II enzyme mutation results in a ≤10-fold increase in drug resistance. Bacteria typically develop mutations in both enzymes as a result of selective pressure for increased resistance, often resulting in resistance levels of 10 to 100 fold higher than the original strain.[244-249]

In similar studies, mutations have identified in both DNA gyrase and topoisomerase IV subunits as contributing to quinolone resistance in bacteria. However, the most commonly altered amino acids are the serine and acidic residues involved in attaching the water-metal ion bridge.[244,250-252] These mutations are thought to cause the breakdown of the bridge and ultimately lead to quinolone resistance.

Studies conducted also indicate that in both laboratory and clinical isolates, over 90% of the mutant pool responsible for quinolone resistance involves changes at the serine residue. Changes at the acidic residue account for the majority of the remaining mutations.[249-250] In general, in the absence of medicines, mutant topoisomerase IV and gyrase maintain wild-type DNA cleavage activity.[253-255] However, at clinically significant concentrations, quinolones do not significantly raise the levels of enzyme-mediated DNA breakage.[256-260] Quinolones lose a lot of their ability to inhibit DNA ligation or to form stable ternary enzyme-DNA-drug complexes, and drug-enzyme binding is also significantly diminished.[261-264]

Mutations in DNA gyrase and topoisomerase IV at the serine residue, which confer resistance to quinolone, do not appear to have a negative impact on catalytic function when no medication is present as stated by studies.[253,255,264] On the other hand, changes to the acidic residue cause a 5–10-fold reduction in overall catalytic activity.[254,265]

This may partly account for the relatively high frequency of the serine mutation's discovery. Almost all bacterial species share a serine residue. This raises the question of why a specific amino acid residue in DNA gyrase and topoisomerase IV, which seemingly has no other function than conferring susceptibility to a particular class of synthetic antibiotics, is so consistently conserved across bacterial species. A study on the antibiotic nybomycin, which is made by the bacterium Streptomyces spp. In *S aureus* strains expressing wild-type gyrase, nybomycin does not have much effect. However, strains expressing a Ser/Leu quinolone-resistant GyrA are resistant to nybomycin.[266] The conserved serine residue in DNA gyrase and topoisomerase IV may represent a "resistance mutation" that provides protection against naturally occurring antibiotics.

2.9.2 Plasmid-Mediated Quinolone Resistance

Recent research has revealed that plasmids carrying quinolone resistance genes are an emerging clinical issue that typically results in low-level (10-fold) resistance.[207,213,218,267-271] However, reports of resistance up to 250-fold have been discovered.[207,244,270] Plasmid-mediated quinolone resistance can be transmitted both vertically and horizontally (via bacterial conjugation), in contrast to target-mediated resistance, which is inherited only vertically across generations. Plasmids that confer

quinolone resistance usually carry genes that also confer resistance to multiple classes of drugs.[207,213,268-269]

Quinolone resistance mediated by plasmids is linked to three gene families. The Qnr genes are responsible for producing proteins from the pentapeptide repeat protein family that are approximately 200 amino acids long.[207,269,272-273] Since their discovery, almost 100 Qnr variations have been categorized into at least five different subfamilies.[207,218,274-275] These proteins are homologous to the DNA mimics McbG and MfpA.[207,269,272] Quinolone resistance appears to be conferred by the Qnr proteins via two distinct pathways. Similar to McbG and MfpA, Qnr genes decrease the DNA binding of gyrase and topoisomerase IV by decreasing the number of available enzyme targets on the chromosome, which offers protection against quinolones. In addition, they bind to topoisomerase IV and DNA gyrase, which prevents quinolones from entering the cleavage complexes generated by the enzyme.[272,273,276-277]

Aac(6′)-Ib-cr is the second plasmid-encoded protein linked to quinolone resistance.[278-279] The aminoglycoside acetyltransferase variant that makes up this protein carries the W102R and D179Y point mutations. Norfloxacin and ciprofloxacin's C7 piperazine ring's unsubstituted nitrogen is acetylated by the enzyme, which reduces the drug's action. Studies conducted have revealed that while both wild-type and mutant aminoglycoside acetyltransferases have the ability to acetylate other medications, only the mutant enzyme is effective against quinolones.[278-279]

Efflux pumps make up the third class of quinolone resistance proteins encoded via plasmids. Three have been determined thus far: QepA1, QepA2 and OqxAB.[207,280-281] The OqxAB protein is mainly detected in animal infections, while the latter two proteins have been found in human bacterial infections.[207,282-283]

Most importantly the simple Darwinian selection controls the distribution of resistance genes in bacterial populations. The use of antibiotics results in the propagation of resistance genes because bacteria with resistance genes reproduce more quickly under antibiotic treatment than do susceptible bacteria. Plasmids can hasten the emergence of novel kinds of resistance by serving as evolutionary catalysts. This happens because bacteria typically possess many copies of plasmids. This enables plasmid-borne resistance genes to rapidly acquire novel functions, in this case the capacity to breakdown antibiotics. Furthermore, plasmids automatically increase the quantity of copies of these updated resistance genes.[284]

2.9.3 Chromosome-Mediated Quinolone Resistance

The conflicting effects of pump-mediated efflux and diffusion-mediated drug uptake control the cellular concentration of quinolones. In contrast to Gram-positive organisms, Gram-negative bacteria possess an extra layer, the outer membrane, which medications must penetrate to enter the cell. Porins are a class of protein channels that allow drug inflow in Gram-negative organisms. Low-level resistance to quinolones may result from downregulating the expression of porins.[207,269,286-287]

Resistance to quinolones can arise from either the overexpression of efflux pumps encoded by the chromosome or the acquisition of efflux pumps encoded by plasmids. Most frequently, mutations in regulatory proteins are to blame for the overexpression of these pumps.[207,287-288] Changes in the absorption and retention of quinolones usually lead to low-level resistance, which is not a major concern in clinical settings without the presence of additional resistance mechanisms (Poole 2007). However, reducing the cellular concentration of quinolones can facilitate the development and transmission of other types of resistance.[213,270,289-290]

CHAPTER III

3.0Materials and Methods

3.1. Study Group

This investigation was done in Near East University Hospital, for this retrospective study, a total of 289 samples were obtained from hospitalized patients (inpatients and outpatients) in different departments of the Hospital starting from 11th June 2020 - 6th June 2022. These include patients from OPD, ICU, CCU, Emergency and different general wards (Chest Disease, oncology, neurology, gastroenterology, cardiology, general wards of male and female etc.). The study protocol was accepted by the Institutional review boards of Near East University. *E coli*, *K pneumoniae* and *P mirabilis* were obtained from separate clinical specimens and different patients both old and young were included in this investigation and repeated isolates were removed from the same clinical specimen of the same patient.

3.2 Tools

- Antec® medical petri-dish
- Test-tubes
- Test-tube rack
- Spatula
- Syringe
- pH meter
- 1000mL conical flask
- Inoculating pin
- Sterile swab stick
- Measuring ruler and marker
- Autoclaving masking tape
- Biosafety cabinet (HERASAFE® KS. Biomedical 2172)
- Vortex-genie 2 (VELP® Scientific. Code F20220176. Made in Europe)
- Photoelectric calorimeter (Densichek® Plus. Biomerieux)
- Weighing balance (Shimadzo. ELB300. Biomedical 2205)
- Vitek 2® compact system (BioMerieux, France)
- Gram negative Vitek 2® ID card – BioMerieux Inc, France.
- Enteric Vitek 2® AST N345 Card- BioMerieux Inc, France.
- Urine Enteric Vitek 2® AST N345 Card- BioMerieux Inc, France.

- Automatic pipette (Gilson Pipetman® .Dk60063, Biomedical 2179. France)
- Surgical-field autoclave (model M50D)
- Autoclave (model OT40L. Miive Steam Art®. Biomedical 2189)
- Incubator (Heraeus® Thermo Scientific. Biomedical 2184)
- Microscope Slides
- Electronic microscope
- Blood culture bottle BD BACTEC (Becton, Dickinson® and company
- BD BACTEC 9120 machine
- Dish washer (LANCER®)
- Refrigerator (SANYO® Medicool. Biomedical 2170)

3.2.1 Equipment

Vitek 2® Compact Machine (Biomerieux)

The VITEK 2® compact device is effective in improving patient outcomes by providing reliable microbial identification (ID) and antibiotic susceptibility testing (AST). It also enhances laboratory capabilities by reducing hands-on time and enabling rapid reporting.

Figure 11

Image of a VITEK 2® compact machine from the company "BIOMERIEUX" (from Near East University laboratory).

BD Bactec® 9120 Machine

BD 9000 system offers a unique, reliable, safe, shorter service, shorter protocol and higher recovery rate than any other blood culture system.

Figure 12

Automated BD BACTEC® 9120 machine (from Near East University laboratory).

Figure 13

BACTEC® 9120 station showing the blood cultured bottles. (From Near East University laboratory).

3.2.2 Kits and Chemicals

- Disinfectant agent (ethanol)
- Saline solution (Biomerieux® SA. REF. V1204. LOT. C0265. France)
- Blood agar- Becton- Dickinson® and company, France.
- Eosin Methylene Blue (EMB) Agar- Becton, Dickinson® and company, France.
- Mueller-Hinton Agar- Becton, Dickinson® and company, France.

3.2.3. Microbiological Media

Media used in this work include; Blood agar, EMB agar and Muller Hinton agar.

40g of Blood agar was weighed for 1000ml of distilled water and 37.4g of EMB agar was weighed for 1000ml of distilled water which were each placed in a sterile conical flask of 1000ml and 1000ml respectively, after properly mixed, the solution was sterilized with an autoclave for 15 minutes at 15lbs pressure (121oC). It was allowed to cool for 40oC and the sterile media was poured in a non-partitioned petri dish and allowed to gel for isolation of the bacteria.

3.2.4. Inclusion Criteria

Data of Patients aged 0-95 were entered in this investigation indicating that there was no restriction to the age limits. Samples such as yeast culture, urine, aspirate, vaginal swab, abscesses/wound scrapings, liquid, sputum, catheter tip, blood and others known to be colonizers for *E coli, K pneumonia* and *P mirabilis* species were taken into consideration.

3.2.5. Exclusion Criteria

For the purpose of this study, there were cases of repeated cultures where isolates that were not identified as *E coli*, *K pneumonia* and *P mirabilis* were discarded.

3.2.6. Colony Morphology

Culture characteristics of K pneumonia isolates were considers as, Color (Lactose fermenting), Consistency (Mucoid), Size (Moderate, Large size), Form (Circular, Irregular), Elevation (Domeshaped, convex, spreader) and Margins (Curled, lobated and entire).

3.3. Identification and Antibiotic Susceptibility Test (AST).

Bacterial identification and ASTs were performed by full automated system Phoenix 100 (Becton Dickinson, Sparks MD®, USA) in line with the manufacturer's recommendations. ID-GNB cards were used to identify isolates using the VITEK 2® system, 64-well plastic ID-GNB cards were used which comprises of forty-one examinations, like eighteen sugar assimilation tests, eighteen sugar fermentation tests, two decarboxylase tests and three miscellaneous tests for urease, utilization of malonate and tryptophane deaminase.

Susceptibility testing using this system were conducted using AST cards, as directed by the manufacturer. The following antimicrobial agents (as dehydrated compounds) are present on the 64-well AST card at the concentrations indicated: gentamicin 32 µg per ml, imipenem, 10 and 16 µg per ml, meropenem 16 µg per ml, piperacillin-tazobactam 128 µg per ml, cefepime 16 µg per ml, ceftazidime 32 µg per ml, ciprofloxacin 4 µg per ml, Ticarcillin-Clavulanate, Cefoperazone-Sulbactam, Tigecycline, Netilmicin, Nitrofurantoin, Fosfomycin w/G6p, Trimethoprim-Sulfamethoxazole, Colistin; Aztreonam, Ceftriaxone, Ertapenem, Amikacin 30µg, Amoxicillin-Clavulanate (f).

The European Committee on Antimicrobial Susceptibility Testing (EUCAST) criteria were used to assess the antibiotic susceptibility testing (AST) results.[291]

3.4 Statistical Analysis

Qualitative and quantitative data values along with the percentage and mean ±standard deviation (SD) is represented as frequency. The Chi-square test is tested as appropriate on the association between two or more variables. Pictorial explanations of the major results of the study were rendered using an appropriate statistical graph. SPSS version 25.00 statistical packages were used for all statistical analysis (SPSS Inc. Chicago, IL, USA). Significance level was accepted to be 0.05.

3.5 Ethical Approval

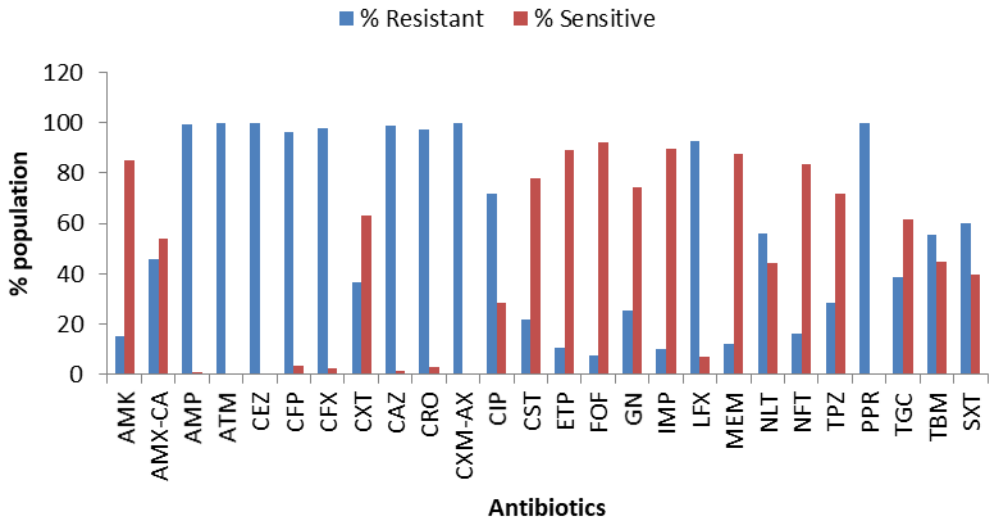
The institutional review boards of near east university hospital gave their approval to the study protocol (2021/88). (Appendix-1).

CHAPTER IV

Results

Figure 14

Overall percentage composition of resistant and sensitive patients to various antibiotics test during the period of study.



In the figure 14, shows the general antibiotic resistance and susceptibility of the total number of samples collected. The highest resistance were ATM, CEZ and piperacillin at 100% respectively while the highest sensitivity was fosfomycin (92.3%).

Table 2

Distribution of clinical samples according to different age groups.

Age	Number	%
0 -18	29	10.1
19 -65	102	35.5
66 -above	156	54.4
Total	**287**	**100%**

Table 2, shows the age distribution according to different age group, the highest percentage of samples was seen amongst the age group of 66 years (54.4%) above while the lowest was seen amongst the age group of 0-18 years of age (10.1%).

Figure 15

The effect of Age (0-18) on the resistant and sensitive patient to various antibiotics test during the period of study.

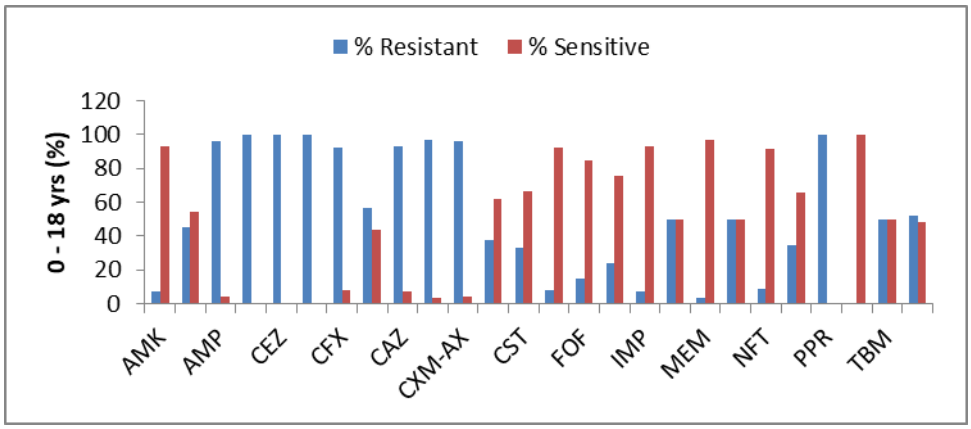


Figure 16

The effect of Age (19-65) on the resistant and sensitive patient to various antibiotics test during the period of study.

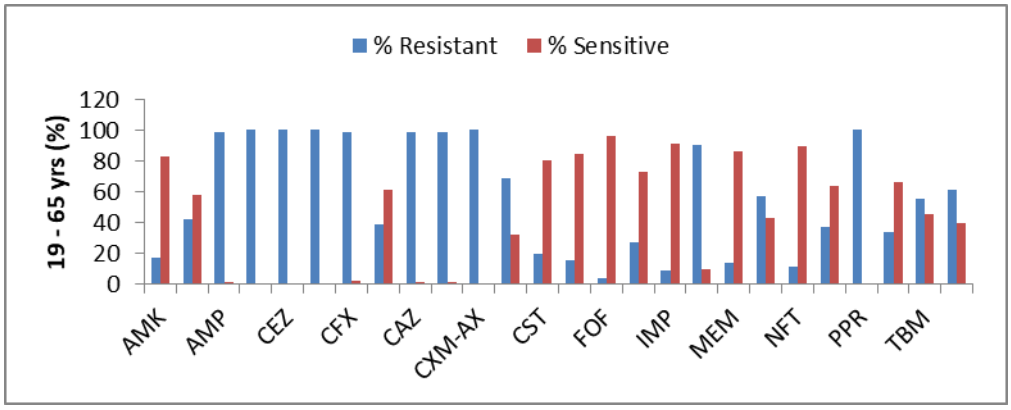


Figure 17

The effect of Age (66-above) on the resistant and sensitive patient to various antibiotics test during the period of study.

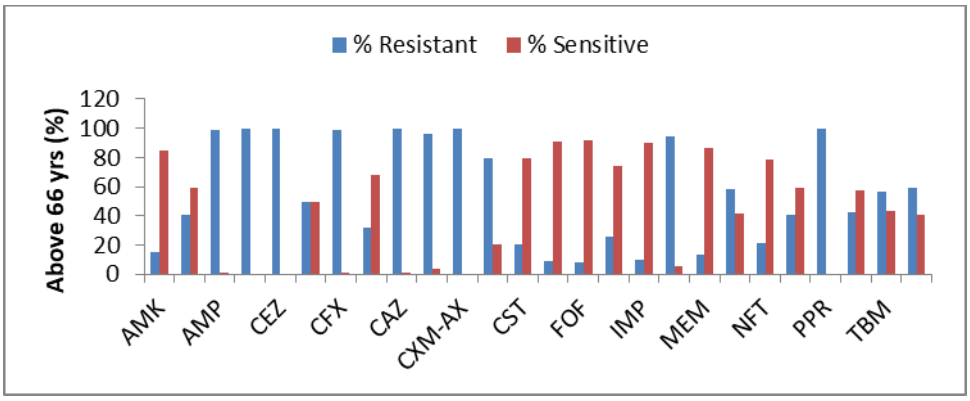


Figure 15-17 shows the effect of age on the resistance and sensitivity of patients in various antibiotic tests. 0-18years patients showed highest antibiotic resistance to ATM (100%), CEZ (100%), CFP (100%) and PPR (100%) respectively while the sensitivity was MEM with (96.4%). Age 19-65years, showed highest antibiotic resistance to ATM (100%), CEZ (100%), CFP (100%), CXM-AX (100%) and PPR

(100%) respectively while the highest sensitivity was FOF (96.2%). Patients above 66years recorded the highest antibiotic resistance at ATM (100%), CEZ (100%) CXM-AX (100%), PPR (100%) respectively while the highest sensitivity was FOF (91.7%).

Table 3

Distribution of clinical samples based on gender.

Gender	Number	%	*E coli*	*K pneumonia*	*P mirabilis*
Male	95	33.1	60	34	1
Female	192	66.9	126	60	6
Total	**287**	**100**	**186**	**94**	**7**

Table 3 shows the distribution of clinical samples based on gender. The male patients had 33.1% of Enterobacteriacea samples collect while the female patients had the highest (66.9%) Enterobacteriacea samples.

Figure 18

Antibiotic resistance and sensitivity representation according to male

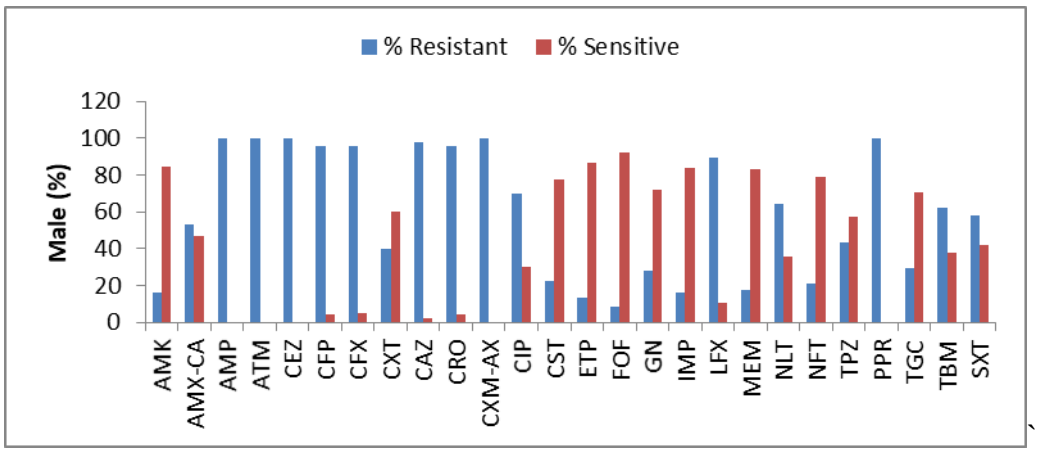


Figure 19

Antibiotic resistance and sensitivity representation according to female

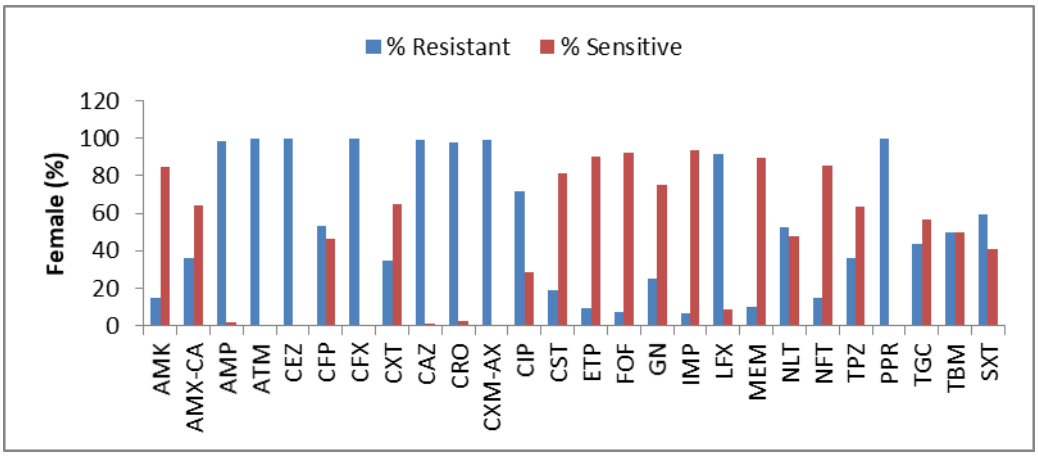


Figure 18-19 shows the effect of gender on the resistance and sensitivity of patients in various antibiotic tests. The highest antibiotic resistance for the male patients were AMP (100%), ATM (100%), CEZ (100%), CXM-AX (100%) AND PPR (100%) respectively while the highest sensitivity was FOF (91.8%). For the female patients, the highest antibiotic resistance were ATM (100%), CEZ (100%), CFP (100%) AND PPR (100%) respectively while the highest sensitivity was IMP (93.5%).

Figure 20

Antibiotic representation for ICU department.

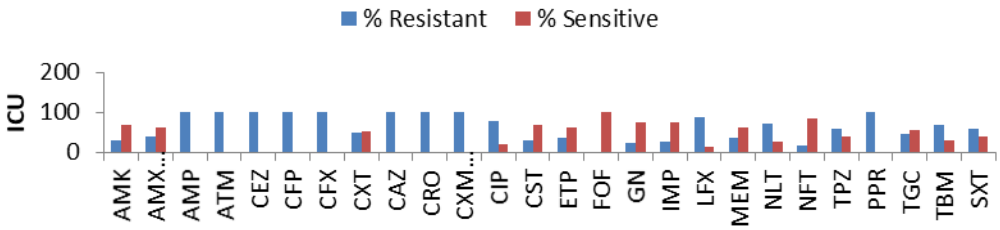


Figure 21

Antibiotic representation for Brain surgery department.

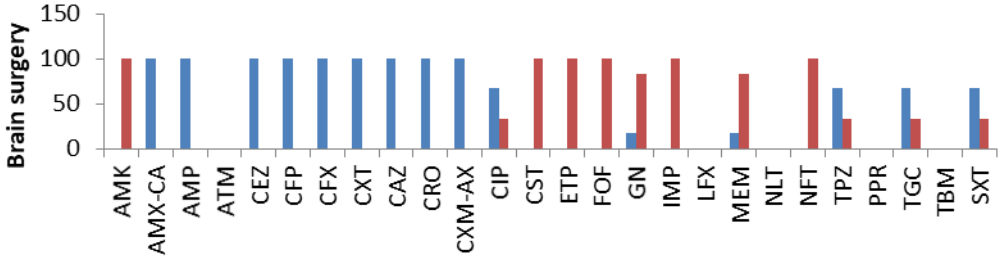


Figure 22

Antibiotic representation for Cardiology department.

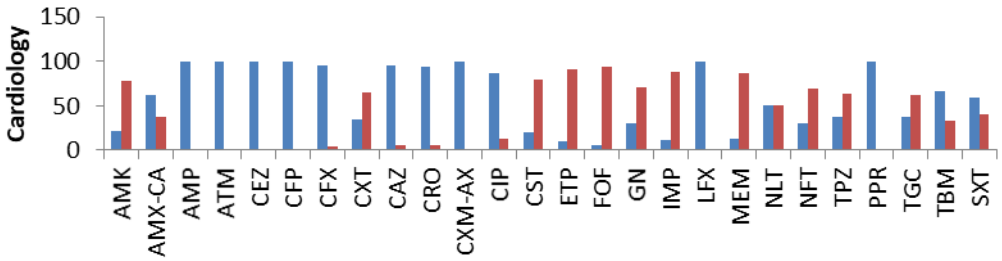


Figure 23

Antibiotic representation for Chest disease department.

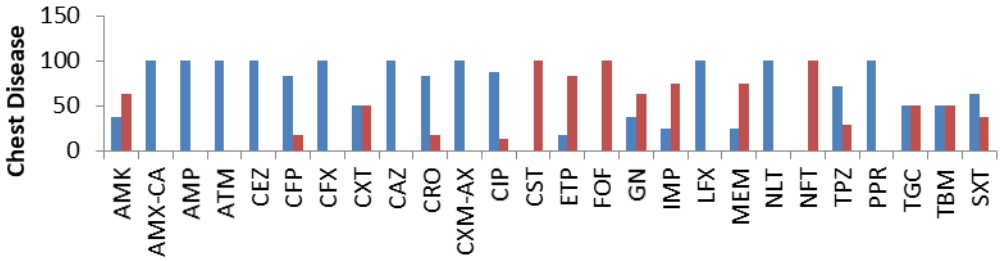


Figure 24

Antibiotic representation for Child health and diseases department.

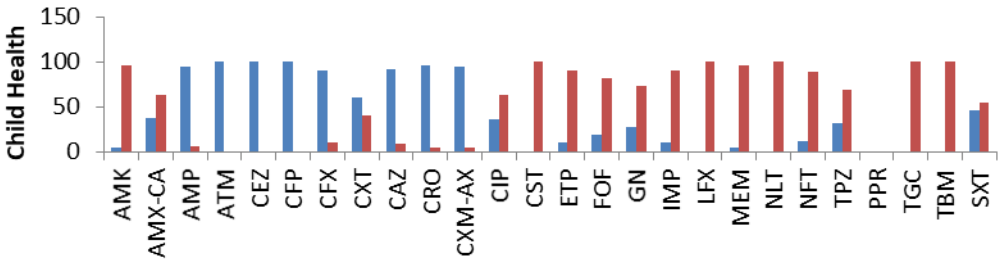


Figure 25

Antibiotic representation for Emergency department.

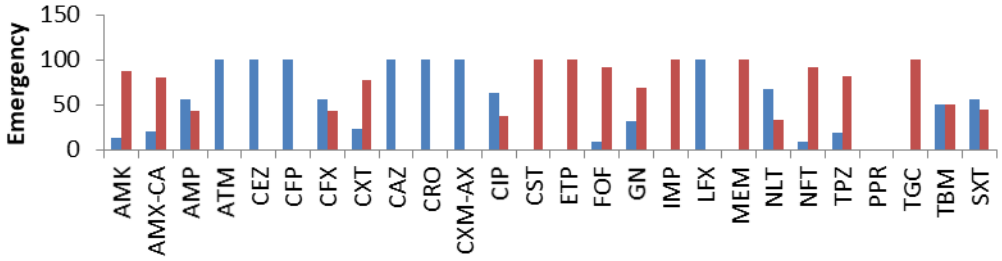


Figure 26

Antibiotic representation for General surgery department.

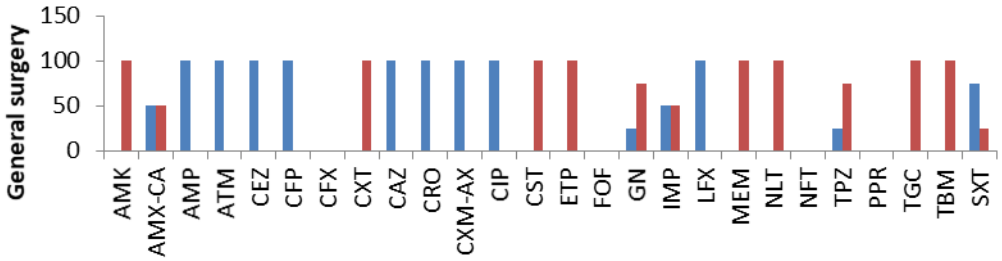


Figure 27

Antibiotic representation for Geriatrics department.

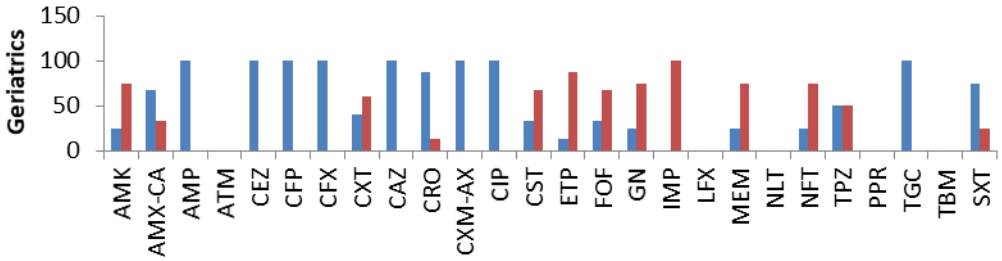


Figure 28

Antibiotic representation for Infection department.

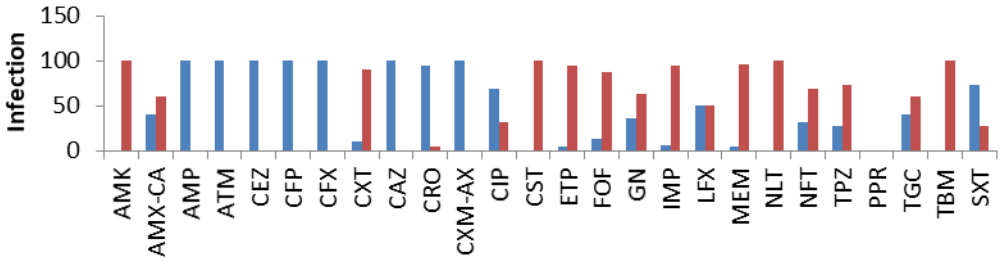


Figure 29

Antibiotic representation for Internal medicine department.

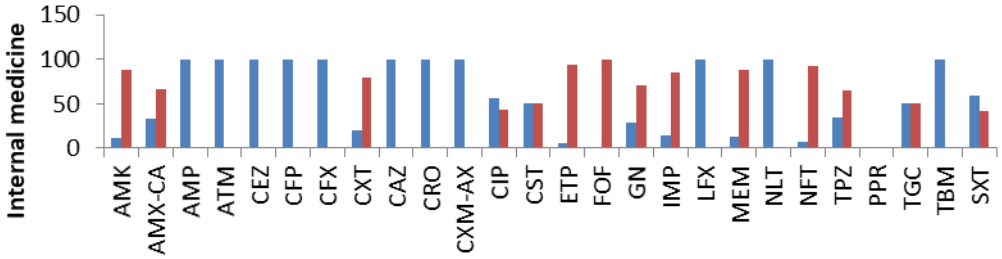


Figure 30

Antibiotic representation for Laboratory department.

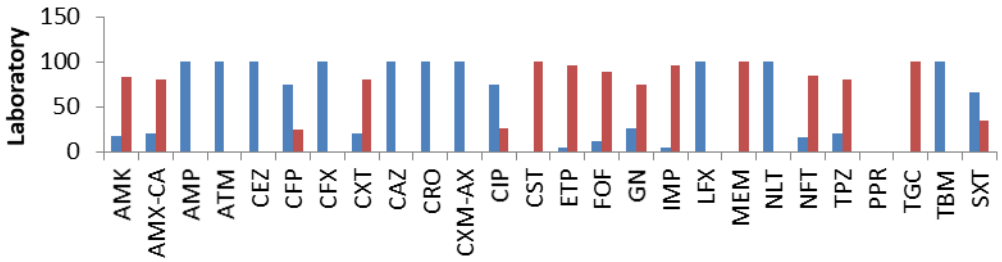


Figure 31

Antibiotic representation for Nephrology department.

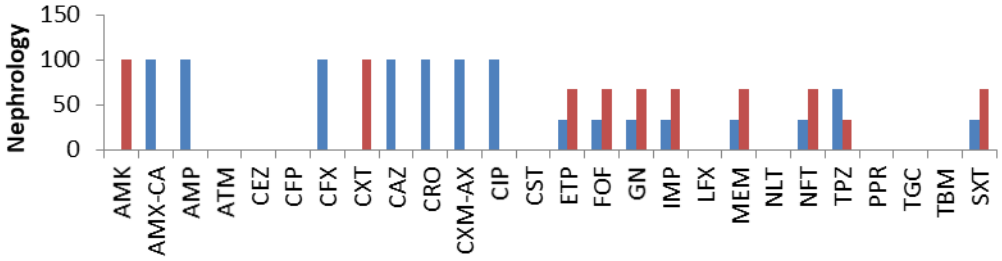


Figure 32

Antibiotic representation for Neurology department.

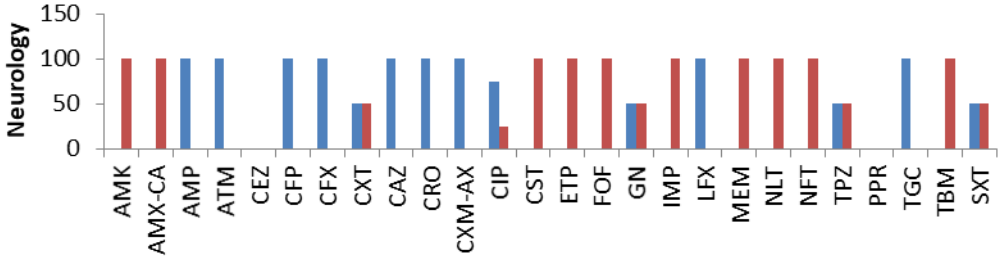


Figure 33

Antibiotic representation for Obstetrics department.

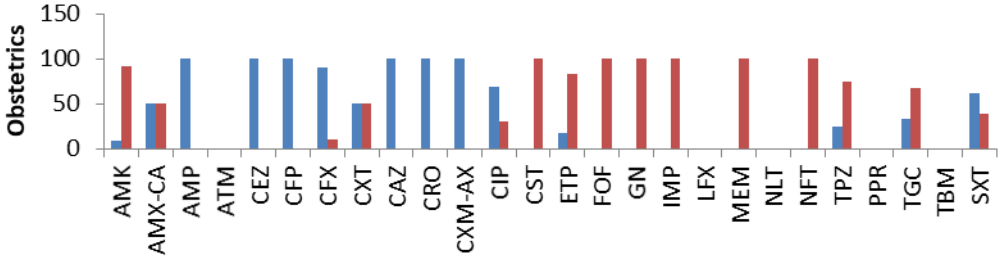


Figure 34

Antibiotic representation for Oncology department.

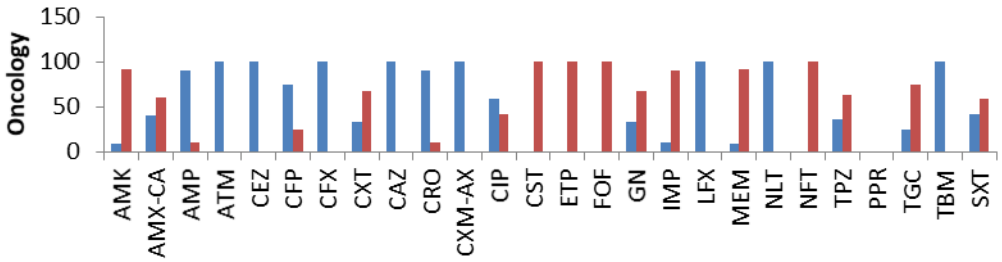


Figure 35

Antibiotic representation for Orthopedic department.

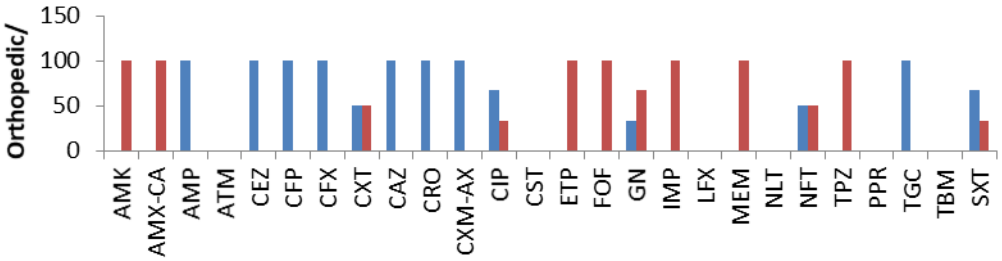


Figure 36

Antibiotic representation for Urology department.

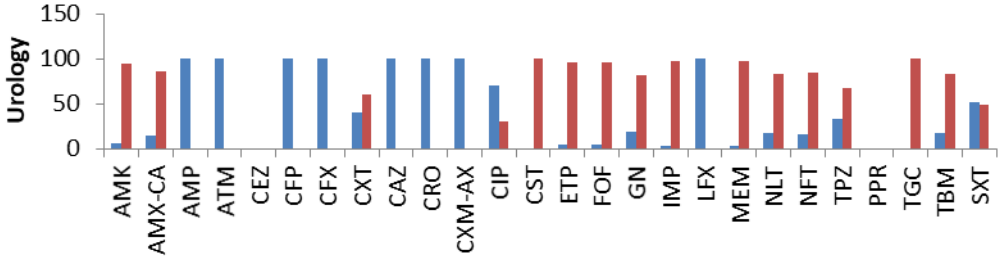


Figure 37

Antibiotic representation for Other department.

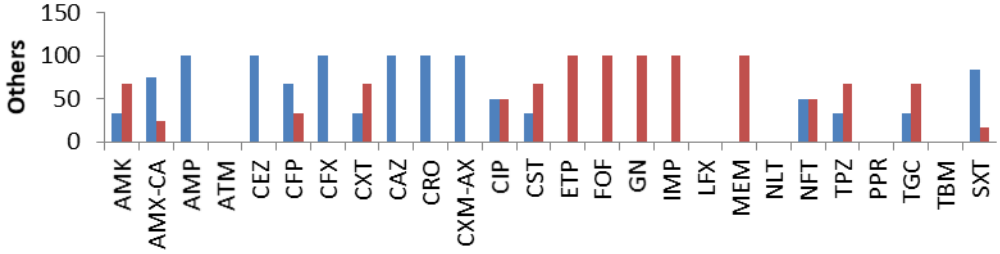


Figure 20-37 shows the antibiotic representation according to hospital departments. In ICU, the highest antibiotic resistance were AMP (100%), ATM (100%), CEZ (100%), CFP (100%), CAZ (100%), CRO (100%), CXM-AX (100%) and PPR (100%) respectively while the highest sensitivity NFT (83.3%).

For brain surgery department, the highest antibiotic resistance were AMX-CA (100%), AMP (100%), CEZ (100%), CFP (100%), CFX (100%), CXT (100%), CAZ (100%), CRO (100%) and CXM-AX (100%) respectively while the highest sensitivity were AMK (100%), CST (100%), ETP (100%), FOF (100%), IMP (100%) and NFT (100%).

For Cardiology department, the highest antibiotic resistance were AMP (100%), ATM (100%), CEZ (100%), CFP (100%), CXM-AX (100%), LFX (100%) and PPR (100%) respectively while the highest sensitivity was FOF (94.4%).

In Chest disease, the highest antibiotic resistance were AMX-CA (100%), AMP (100%), ATM (100%), CEZ (100%), CFX (100%), CAZ (100%), CXM-AX (100%), LFX (100%) and NLT (100%) respectively while the highest sensitivity were CST (100%), FOF (100%) and NFT (100%).

For Child health and diseases department, the highest antibiotic resistance were ATM (100%), CEZ (100%) and CFP (100%) respectively while the highest sensitivity were CST (100%), LFX (100%), NLT (100%), TGC (100%) and TBM (100%).

In Emergency department, the highest antibiotic resistance were ATM (100%), CEZ (100%), CFP (100%), CAZ (100%), CRO (100%), CXM-AX (100%) and LFX (100%) respectively while the highest sensitivity were CST (100%), ETP (100%), IMP (100%), MEM (100%) and TGC (100%).

For General surgery department, the highest antibiotic resistance were AMP (100%), ATM (100%), CEZ (100%), CFP (100%), CAZ (100%), CRO (100%), CXM-AX (100%), CIP (100%) and LFX (100%) respectively while the highest sensitivity were AMK (100%), CXT (100%), CST (100%), ETP (100%), MEM (100%), NLT (100%), TGC (100%) and TBM (100%).

For Geritatrics department, the highest antibiotic resistance were AMP (100%), CEZ (100%), CFP (100%), CFX (100%), CAZ (100%), CXM-AX (100%), CIP (100%) and TGC (100%) respectively while the highest sensitivity were IMP (100%).

For Infectious disease department, the highest antibiotic resistance were AMP (100%), ATM (100%), CEZ (100%), CFP (100%), CFX (100%), CAZ (100%) and

CXM-AX (100%) respectively while the highest sensitivity were AMK (100%), CST (100%), NLT (100%) and TBM (100%).

In Internal medicine department, the highest antibiotic resistance were AMP (100%), ATM (100%), CEZ (100%), CFP (100%), CFX (100%), CAZ (100%), CRO (100%), CXM-AX (100%), LFX (100%), NLT (100%) and TBM (100%) respectively while the highest sensitivity were FOF (100%).

For Laboratory department, the highest antibiotic resistance were AMP (100%), ATM (100%), CEZ (100%), CFX (100%), CAZ (100%), CRO (100%), CXM-AX (100%), LFX (100%), NLT (100%), and TBM (100%) respectively while the highest sensitivity were CST (100%), MEM (100%) and TGC (100%).

In Nephrology department, the highest antibiotic resistance were AMP (100%), ATM (100%), CFP (100%), CFX (100%), CAZ (100%), CRO (100%), CXM-AX (100%), LFX (100%) and TGC (100%) respectively while the highest sensitivity were AMK (100%), AMX-CA (100%), CST (100%), ETP (100%), FOF (100%), IMP (100%), MEM (100%), NLT (100%), NFT (100%) and TBM (100%).

In Obstetrics department, the highest antibiotic resistance were AMP (100%), CEZ (100%), CFP (100%), CAZ (100%), CRO (100%) and CXM-AX (100%) respectively while the highest sensitivity were CST (100%), FOF (100%), GN (100%), IMP (100%), MEM (100%) and NFT (100%).

In Oncology department, the highest antibiotic resistance were ATM (100%), CEZ (100%), CFX (100%), CAZ (100%), CXM-AX (100%), LFX (100%), NLT (100%) and TBM (100%) respectively while the highest sensitivity were CST (100%), ETP (100%), FOF (100%), and NFT (100%).

In Orthopedic & traumatology department, the highest antibiotic resistance were AMP (100%), CEZ (100%), CFP (100%), CFX (100%), CAZ (100%), CRO (100%), CXM-AX (100%) and TGC (100%) respectively while the highest sensitivity were AMK (100%), AMX-CA (100%), ETP (100%), FOF (100%), IMP (100%), MEM (100%) and TPZ (100%). In Urology department, the highest antibiotic resistance were AMP (100%), ATM (100%), CFP (100%), CFX (100%), CAZ (100%), CRO (100%), CXM-AX (100%) and LFX (100%) respectively while the highest sensitivity were CXT (100%) and TGC (100%).

For Others (Dermatology, Heamatology, Pediatric surgery, Plastic surgery, Radiology and Rheumatology) departments, the highest antibiotic resistance were AMP (100%), CEZ (100%), CFX (100%), CAZ (100%), CRO (100%) and CXM-AX

(100%) respectively while the highest sensitivity were ETP (100%), FOF (100%), GN (100%), IMP (100%) and MEM (100%).

Table 4

Distribution of samples according to application type.

Application type	Number	%
Inpatient	170	59.23
Outpatient	117	40.77
Total	**287**	**100**

Table 4, shows the distribution of samples according to the In/Out patients. The highest percentage recorded was from In patients (59.2%) while Out patients recorded (40.8%).

Figure 38

Antibiotic resistance and sensitivity representation for Inpatient

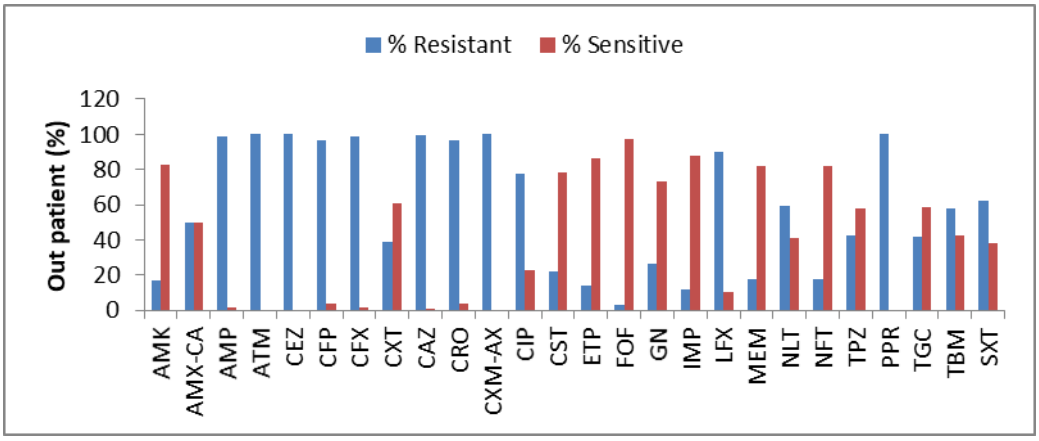


Figure 39

Antibiotic resistance and sensitivity representation for Outpatient

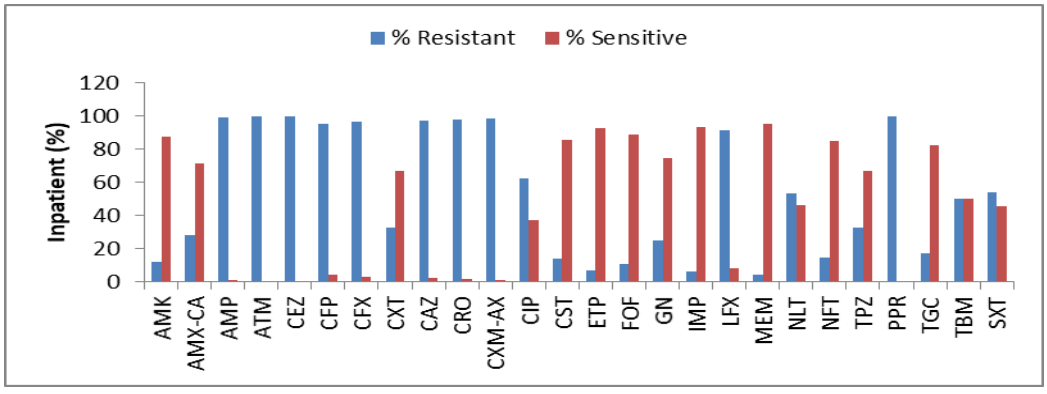


Figure 38-39 shows the antibiotic representation according to patient application types. For in-patient, the highest antibiotic resistance were ATM (100%), CEZ (100%) and PPR (100%) respectively while the highest sensitivity was MEM (95.6%).

For out-patient, the highest antibiotic resistance were ATM (100%), CEZ (100%), CXM-AX (100%) and PPR (100%) respectively while the highest sensitivity was FOF (97%).

Table 5

Number of samples according to different sample type.

Sample type	Number	%	*E coli*	*K pneumonia*	*P mirabilis*
Abscess/ Wound material	18	6.3	10	8	1
Aspiration fluid	26	9.1	8	16	2
Blood	16	5.6	10	6	-
Catheter fluid	4	1.4	-	3	1
Sputum	21	7.3	7	14	-
Urine	200	69.7	151	46	3
Vaginal discharge/Swab	2	0.7	1	1	-
Total	**287**	**100**	**186**	**94**	-

Table 5 shows the different sample types and the Enterobacteriacea isolated from them. The highest was Urine sample (69.7%) while the lowest was discharge/Swab (0.7%).

Figure 40

Antibiotic representation according to sample type.

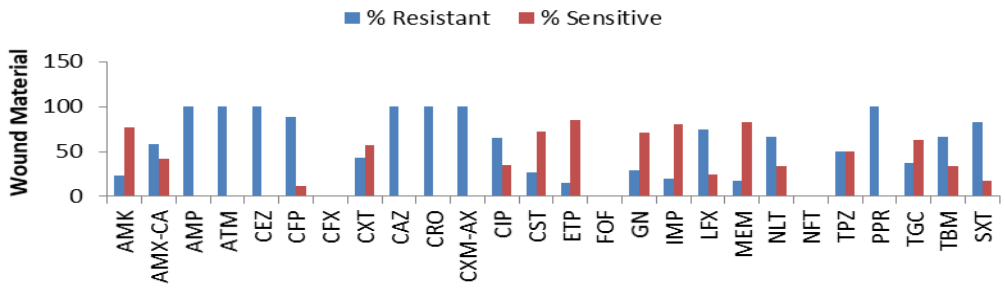


Figure 41

Antibiotic representation according to sample type.

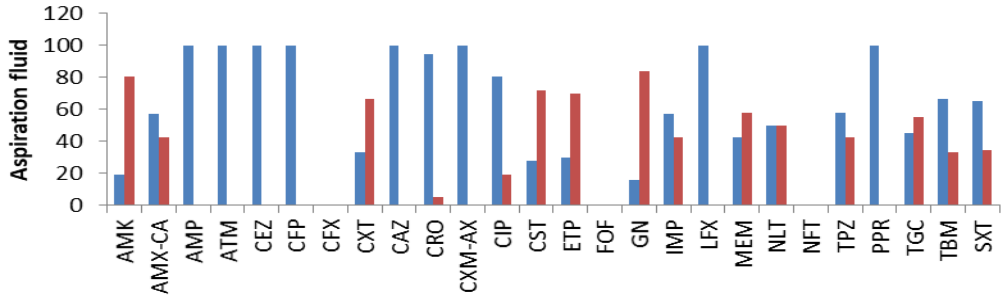


Figure 42

Antibiotic representation according to sample type.

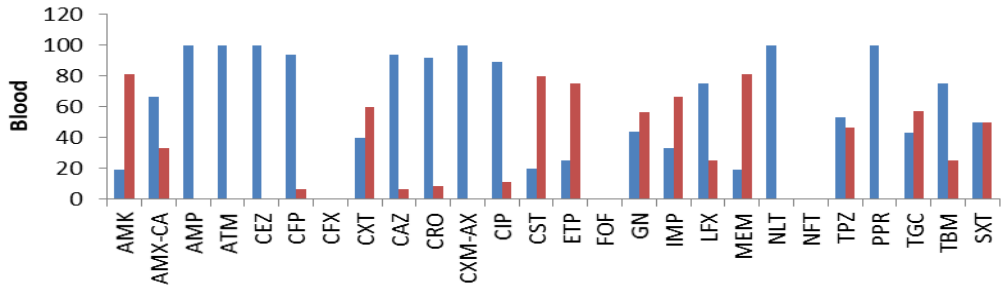


Figure 43

Antibiotic representation according to sample type.

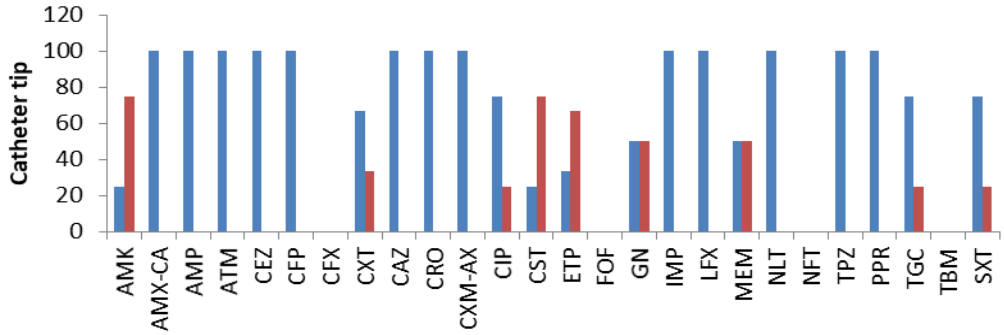


Figure 44

Antibiotic representation according to sample type.

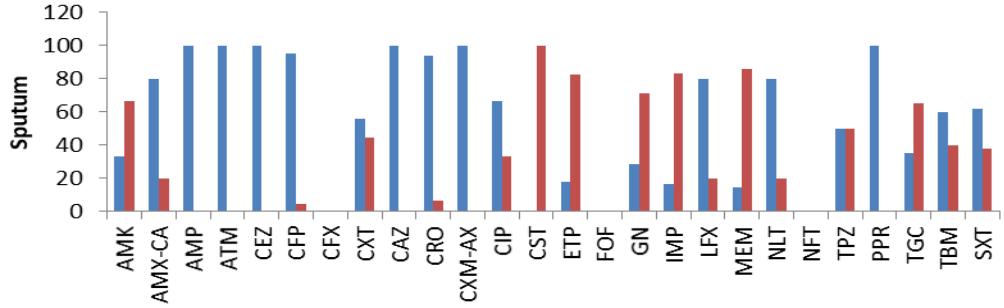


Figure 45

Antibiotic representation according to sample type.

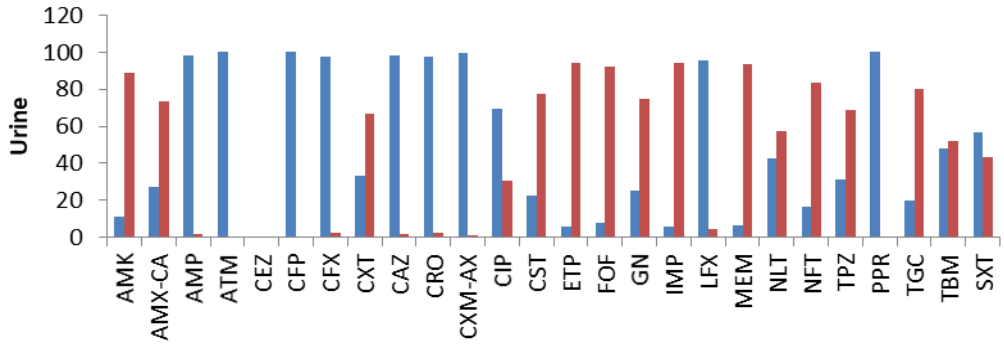


Figure 46

Antibiotic representation according to sample type.

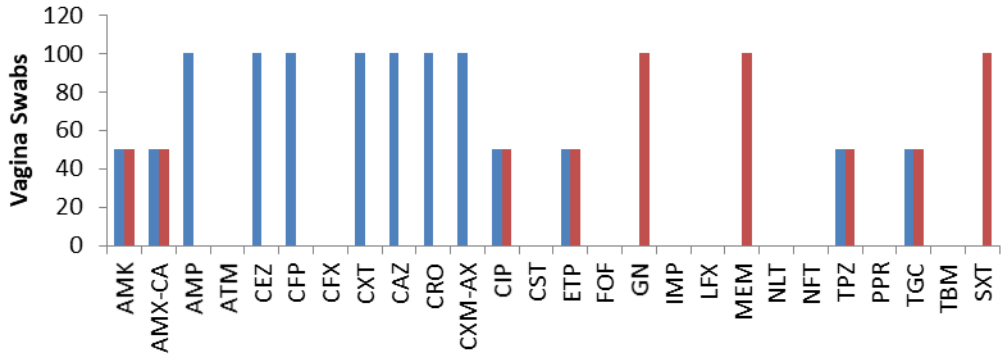


Figure 40-46 shows the antibiotic representation according to sample types. For Abscess/wound material, the highest antibiotic resistance were AMP (100%), ATM (100%), CEZ (100%), CAZ (100%), CRO (100%), CXM-AX (100%) and PPR (100%) respectively while the highest sensitivity was ETP (84.6%).

For Aspiration fluid, the highest antibiotic resistance were AMP (100%), ATM (100%), CEZ (100%), CFP (100%), CAZ (100%), CXM-AX (100%), LFX (100%) and PPR (100%) respectively while the highest sensitivity was AMK (80.8%).

For Blood, the highest antibiotic resistance were AMP (100%), ATM (100%), CEZ (100%), CXM-AX (100%), NLT (100%) and PPR (100%) respectively while the highest sensitivity were MEM (81.3%) and AMK (81.3%).

For Catheter tip, the highest antibiotic resistance were AMX-CA (100%), AMP (100%), ATM (100%), CEZ (100%), CFP (100%), CAZ (100%), CRO (100%), CXM-AX (100%), IMP (100%), LFX (100%), NLT (100%), TPZ (100%) and PPR (100%) respectively while the highest sensitivity was AMK (75%).

For Sputum, the highest antibiotic resistance were AMP (100%), ATM (100%), CEZ (100%), CAZ (100%), CXM-AX (100%) and PPR (100%) respectively while the highest sensitivity was MEM (85.7%).

For Urine, the highest antibiotic resistance were ATM (100%), CFP (100%) and PPR (100%) respectively while the highest sensitivity was ETP (94.3%).

For Vaginal discharge/Swab, the highest antibiotic resistance were AMP (100%), CEZ (100%), CFP (100%), CXT (100%), CAZ (100%), CRO (100%) and CXM-AX (100%) respectively while the highest sensitivity was GN (100%), MEM (100%). AMK (100%).

Table 6

Percentage Analysis Microorganism detected based on Hospital Department

	Microorganism			
	Escherichia coli	***Klebsiella pneumoniae***	***Proteus mirabilis***	
Units	**N (%)**	**N (%)**	**N (%)**	**Total**
ICU	19 (10.2)	27 (28.7)	2 (28.6)	48
Brain surgery	3 (1.6)	3 (3.2)	Nil	6
Cardiology	26 (14.0)	13 (13.8)	Nil	39
Cardiovascular Surgery	4 (2.2)	3 (3.2)	Nil	7
Chest Diseases and Allergy	1 (0.5)	7 (7.4)	Nil	8
Child Health and Diseases	13 (7.0)	9 (9.6)	Nil	22
Dermatology	Nil	1 (1.1)	Nil	1
Emergency	13 (7.0)	3 (3.2)	Nil	16
General Surgery	4 (2.2)	Nil	Nil	4
Geriatrics	5 (2.7)	2 (2.1)	1 (14.3)	8
Haematology	1 (0.5)	Nil	Nil	1

Infectious Disease	10 (5.4)	3 (3.2)	1 (14.3)	14
Internal medicine	13 (7.0)	3 (3.2)	2 (28.6)	18
Laboratory	18 (9.7)	4 (4.3)	1 (14.3)	23
Nephrology	2 (1.1)	1 (1.1)	Nil	3
Neurology	3 (1.6)	1 (1.1)	Nil	4
Obstetrics	11 (5.9)	2 (2.1)	Nil	13
Oncology	11 (5.9)	1 (1.1)	Nil	12
Orthopaedics and Traumatology	1 (0.5)	2 (2.1)	Nil	3
Paediatric Surgery	1 (0.5)	Nil	Nil	1
Plastic surgery	Nil	1 (1.1)	Nil	1
Radiology	1 (0.5)	Nil	Nil	1
Rheumatology	1 (0.5)	Nil	Nil	1
Urology	25 (13.4)	8 (8.5)	Nil	33
Aggregate	**186 (100.0)**	**94 (100.0)**	**7 (100.0)**	**287**

*N = Number

Table 6 revealed that the highest number of *E coli* 26 (14%) was discovered in cardiology department; the highest number of *K pneumoniae* 27 (28.7%) was discovered in ICU department; and the highest prevalence of *P mirabilis* 2 (28.6%) was also discovered in ICU department.

Figure 47

Percentage Analysis of the isolated microorganism from laboratory tests.

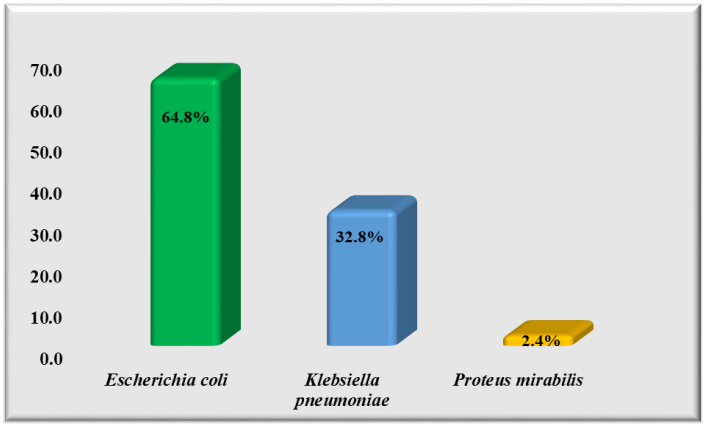


Figure 16 revealed that majority of the microorganisms isolated was *E coli* (64.8%), followed by *K pneumonia* (32.8%) and *P mirabilis* (2.4%).

Figure 48

Antibiotic representation for Escherichia coli.

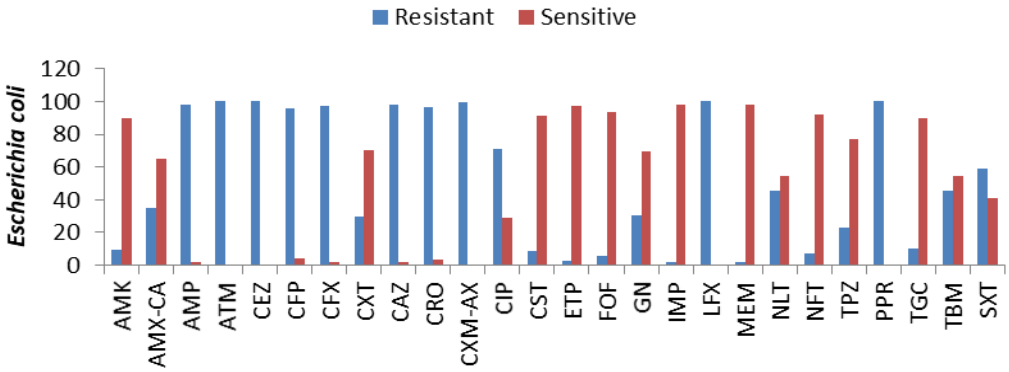


Figure 49

Antibiotic representation for Klebsiella pneumonia.

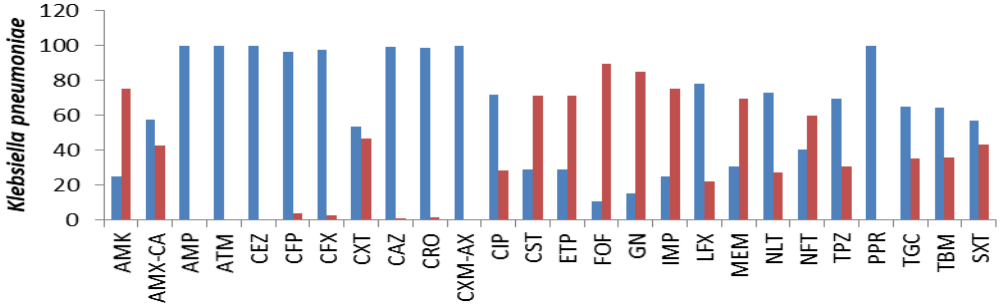


Figure 50

Antibiotic representation for Proteus mirabilis.

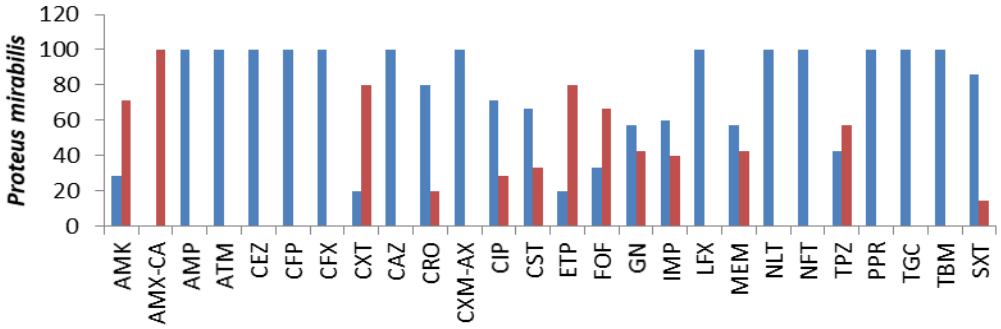


Figure 47-49 shows the antibiotic representation according to Microorganism. For E coli, the highest antibiotic resistance were ATM (100%), CEZ (100%), LFX (100%) and PPR (100%) respectively while the highest sensitivity was IMP (98.1%).

For K pneumonia, the highest antibiotic resistance were AMP (100%), ATM (100%), CEZ (100%), CXM-AX (100%) and PPR (100%) respectively while the highest sensitivity was FOF (89.2%).

For P mirabilis, the highest antibiotic resistance were AMP (100%), ATM (100%), CEZ (100%), CFP (100%), CFX (100%), CXM-AX (100%), LFX (100%), NLT (100%), PPR (100%), TGC (100%) and TBM (100%) respectively while the highest sensitivity was AMX-CA (89.2%).

Figure 51

Antibiotic comparison of non-ICU patients.

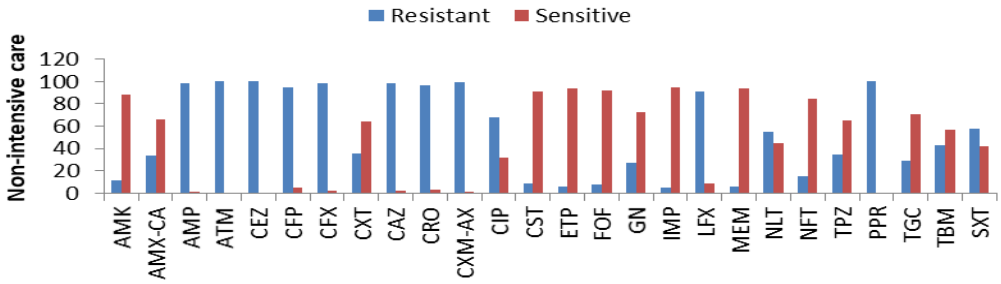


Figure 52

Antibiotic comparison of ICU.

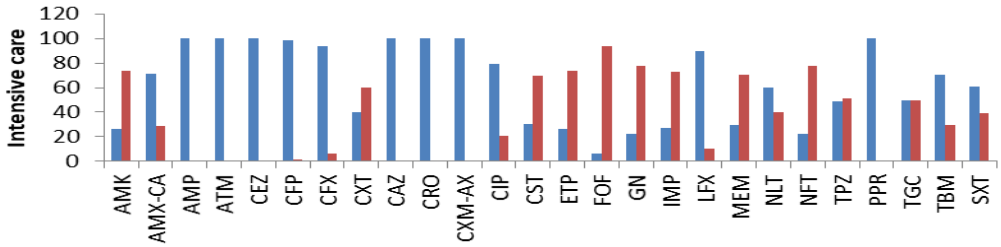


Figure 50-51 shows the antibiotic representation according to ICU and non-ICU. In ICU, the highest antibiotic resistance were AMP (100%), ATM (100%), CEZ (100%), CAZ (100%), CRO (100%), CXM-AX (100%) and PPR (100%) respectively while the highest sensitivity FOF (93.3%). For non-ICU, the highest antibiotic resistance were ATM (100%), CEZ (100%) and PPR (100%) respectively while the highest sensitivity IMP (94.9%).

Two hundred and eighty seven ESBL positive isolates; It was isolated from 95 male (33.1%) and 192 female (66.9%) patients. The P-value for ESBL Gender Crosstabulation of male and female is 0.891, with an odd ratio of 0.755 for Quinolone, while for the co-resistance antibiotic Cefazolin has the p-value of 0.016, with an odd ratio of 0.069. There are statistical differences between the co-resistance ESBL antibiotic and Quinolone in gender. According to 287 ESBL isolates; 170 patients were inpatients and 117 patients were outpatients. The ESBL crosstabulations of inpatients and outpatients show P-values (Pearson chi square) = 0.000 and odd ratio = 0.000 for Cefazolin and for Quinolone the P-value is 0.055 and an odd ratio of 0.043 respectively. There are statistical differences between the co-resistance ESBL and the Quinolone antibiotic in inpatient/outpatients. The p-value for ESBL microorganism crosstabulation of Entrobacteriacea is 0.990 with an odd ratio of 0.988 for Quinolone, while for the co-resistance antibiotic cefazolin has the p-value of 0.010 with an odd ratio of 0.011.

CHAPTER V

Discussion

This study evaluated three basic microorganisms, the level of sensitivity, and antibiotic resistance using hospital record. In a cohort of 287 patient receiving medical care in Near East University Hospital. Majority of the patients, were infected with *E coli* (64.8%) which suggests the high incidence of *E coli* infection among these patients.

Enterobacteriaceae causes illnesses and a high prevalence of infection in hospital setting which can lead to the spread of diseases among patients, thereby increasing the risk of outbreaks and further spread of infection to the general public. Antibiotic resistance refers to the ability of microorganisms to resist the effects of antibiotics that were previously effective in treating infections. This occurs because of the prolonged and misuse of antibiotics which increases the rate at which resistance develops.

This research work revealed that there is a high rate of infection in female (66.9%) than in male patients (33.1%), this is in line with the work done by Azargun et al. (2018) which stated that there was a higher infection rate in female (64.4%) than in male patients (35.6%).[293] It also correlates with the work done by Koley et al. (2022) which showed that, samples collected from female patients (60%) revealed higher culture positivity rate than male patients (40%).[294]

In this current study, it was observed that the prevalence ESBL isolates among the in-patients and out-patients was 59.2% and 40.8% respectively. Although the prevalence of ESBL in out-patients is less than in-patients, it is common in communities. This is because ESBL producing *E coli* isolates were widely spread among both in-patients and out-patients. This observation therefore confirms the assertion by Kumal et al. (2014) where in-patients and out-patients was 60.95 and 48%, respectively and strengthens the fact that ESBL producers are indeed as much a problem in the communities as in the hospitals.[295]

From the total number of ESBL samples collected, the highest isolate was from urine (69.7%), followed by Aspirate (8.7%) and the lowest was Vaginal discharge/swab (0.7%). In line with a study by Masoud et al. (2021), the highest prevalence was observed in urine (62%) while the lowest was seen from eye discharge (10%).[296] Similar research by Kumar et al. (2014) noted that ESBL isolates was highest in blood

sample (66.67%) and lowest in sputum (33.33%). This discovery does not entirely tally with this present study.[295]

This current research shows that the most prevalent Enterobacteriacea isolated is *E coli* (64.8%) which was followed by *K pneumonia* (32.8%) and *P mirabilis* (2.4%). This is in line with the study by Azargun et al (2018) which showed that *E coli* was the most common isolate (80.8%), *K pneumonia* (12.8%) and *P mirabilis* (0.9%). This prevalence of ESBL varies depending on species and geographical regions. In South Korea and Iran, 30% and 34.8% of isolates were reported positive for ESBL respectively. While in North America, the prevalence of ESBL-producing *E coli* and *K pneumoniae* was low. However, a high prevalence of ESBL was reported in other countries. Differences between these results may be due to the length of ICU stay, inappropriate and excessive use of antibiotics and length of hospitalization.[293]

Cardiology department recorded the highest number of *E coli* isolates 26 (14%), for *K pneumoniae* 27 (28.7%), the highest number was discovered in ICU department; and the highest prevalence of *P mirabilis* with 42.9% was also discovered in ICU department. Similarly, a number of studies have documented high prevalence of *E coli* and growing resistance. Biedenbach et al. (2014) found a high isolates of *E coli* and the high resistance to antibiotics with elderly patients been more resistant to antibiotics *K pneumoniae*.[297]

It was found that the antibiotic with the highest level of resistance was Ceftazidime, 282 (98.3%) resistance. this was followed by Cefuroxime-axetil (85.7%), Ceftriaxone and Ampicillin (82.2%) and Ciprofloxacin (70.7%) and the lowest resistance fosfomycin (7.7%). This partially correlates with a similar study by Azargun et al (2018), which showed the total resistance rate of Enterobacteriaceae to antimicrobial agents was ceftazidime 174 (79.4%), ciprofloxacin 126 (57.5%) and lowest resistance imipenem 7 (3.2%).[293]

Figure 48-50 revealed that *E coli* has developed 97.8% resistance to Ceftazidime which is not in line with studies carried out by (Kantele et al. 2022 and Ibrahim et al. 2023). Kantele et al. (2022) found that ESBL strain carrying *E coli* showed 0-40% resistance to Azithromycin while Ibrahim et al (2023) discovered a higher percentage resistance where the result revealed that in terms of antibiotic resistance, 97.1% of the isolates were resistant to ampicillin and 71.4% to Ceftazidime.[298-299]

The study results on the phenotypic methods were discovered to be insignificant for the 70.7% of ESBL producing strains (ciprofloxacin P< 0.990). This is not consistent with Leila et al (2009) that states that 41% of ESBL positive strains (P< 0.05) were significant to the resistance of ciprofloxacin.[300]

5.2 CONCLUSION

The emergence and spread of ESBL-producing Enteriobactriacea strains (*E coli*, *K pneumonia* and *P mirabilis*) is worrisome and usage of cephalosporins against these isolates is ineffective. To reduce the development and spread of antibiotic resistance, it is important to use antibiotics appropriately and to reduce the unnecessary use of antibiotics. This includes using antibiotics only when they are needed, using the right antibiotic for the specific infection, the correct dosage and for the recommended duration. Fosfomycin and imipenem are the most effective antibiotics for empirical therapy in our setting. Therefore, detection of PMQR determinants and ESBL genes among non-susceptible fluoroquinolone Enterobacteriaceae is important for appropriate empirical treatment and infection control. Due to importance of ESBL producing organisms and difficult treatment of infections caused by these bacteria, rapid identification of ESBL producing isolates in clinical laboratories should be adopted and laboratory services should be available to support every infection control program.

5.3 PUBLIC HEALTH IMPLICATION OF THE STUDY

This study has important public health implications, as it highlights the increasing problem of antibiotic resistance. The high levels of resistance found for some antibiotics, such as ceftazidine means that these drugs may be less effective for treating infections caused by certain microorganisms. This can lead to longer illness, more severe symptoms, and an increased risk of complications. The study also highlights the importance of using antibiotics appropriately, and avoiding overuse or misuse, to help reduce the development of resistance. Additionally, the results suggest that older patients and those in certain departments, such as the ICU, may be at higher risk of developing antibiotic resistance. This information can be used to develop targeted interventions to prevent the spread of resistance, such as increased infection control measures and improved antibiotic stewardship programs. Overall, the study

highlights the ongoing need for ongoing surveillance of antibiotic resistance and the development of new treatments to address this growing public health challenge.

5.4 RECOMMENDATION

Based on the findings of the study, the following five recommendations can be made:

1. Health care workers and public health expert should encourage the appropriate use of antibiotics. Overuse or misuse of antibiotics is a major contributor to the development of resistance. Effort should be made to prescribe antibiotics only when necessary and to use the right drug, at the right dose, for the right duration.
2. It is important for the hospital to take steps to control the spread of microorganisms in order to prevent future infections, such as implementing proper hygiene and infection control measures, and conducting ongoing monitoring and surveillance
3. There should be constant promote the use of alternative treatments. Where possible, alternative treatments such as probiotics, vaccines, or other therapies, should be used to prevent or treat infections, rather than relying solely on antibiotics.
4. There should be a well targeted interventions for at-risk populations. The study showed that older patients and those in certain departments, such as the ICU, may be at higher risk of developing antibiotic resistance. Targeted interventions, such as increased infection control measures and improved antibiotic stewardship programs, should be implemented in these populations.
5. Government should enhance surveillance of antibiotic resistance. Regular monitoring of antibiotic resistance is critical for detecting trends and guiding the development of new treatments. Recommendations should be made to enhance existing surveillance systems, and to establish new ones where needed.
6. Government and non-governmental organizations should support research into new treatments. The increasing problem of antibiotic resistance highlights the need for continued research into new treatments. Recommendations should be made to support funding for research into new antibiotics, alternative therapies and other treatments to address this growing public health challenge.

REFERENCES

Ehrlich-Biography, P. (1967) Nobel Lectures, Physiology or Medicine 1901-1921. Elsevier Publishing Company, Amsterdam.

Chiang, C.-Y. et al. Mitigating the impact of antibacterial drug resistance through host-directed therapies: Current progress, outlook and challenges. Bio 9, e01932-1917. https://doi.org/10.1128/mBio.01932-17 (2018).

Saipriya, J. B., Shubha, D. S., Sudhindra, K. S., Sumantha, A. & Madhuri, K. R. Clinical importance of emerging ESKAPE pathogens and antimicrobial susceptibility profle from a tertiary care centre. Int. J. Curr. Microbiol. Appl. Sci. 2018. 7, 2881–2891. https://doi. org/10.20546/ijcmas.2018.705.336.

O'Neill, J. Tackling Drug-Resistant Infections Globally: Final Report and Recommendations; Review on Antimicrobial Resistance (Wellcome Trust, London, 2016).

Ye, Q. et al. Characterization of extended-spectrum β-lactamase-producing Enterobacteriaceae from retail food in China. Front. Microbiol. 9, 1709. https://doi.org/10.3389/fmicb.2018.01709 (2018).

Madhi, F. et al. Febrile urinary-tract infection due to extended-spectrum β-lactamase-producing Enterobacteriaceae in children: A French prospective multicenter study. PLoS ONE 13, e0190910. https://doi.org/10.1371/journal.pone.0190910 (2018).

Rajivgandhi, G., Maruthupandy, M., Ramachandran, G., Priyanga, M. & Manoharan, N. Detection of ESBL genes from ciprofoxacin resistant Gram negative bacteria isolated from urinary tract infections (UTIs). Front. Lab. Med. 2, 5–13. http://creativecommons .org/licenses/by-ncnd/4.0/ (2018).

Taghizadeh, S. et al. Epidemiology of extended spectrum β-lactamase producing gram negative bacilli of community acquired urinary tract infection in Tabriz, Iran. J. Res. Med. Dent. Sci. 6, 199–204. https://doi.org/10.24896/jrmds.20186231 (2018).

Iredell J, Brown J, Tagg K. Antibiotic resistance in Enterobacteriaceae: mechanisms and clinical implications. BMJ 2016;352:1, http://dx.doi.org/10.1136/ bmj.h6420.

Xia J, Gao J, Tang W. Nosocomial infection and its molecular mechanisms of antibiotic resistance. Biosci trends 2016;10(1):14–21, http://dx.doi.org/10. 5582/bst.2016.01020.

Chaudhary, U. and Aggarwal, R. (2004) Extended Spectrum Beta-Lactamases (ESBLs)—An Emerging Threat to Clinical Therapeutics. Indian Journal of Medical Microbiology, 22, 75-80.

G. S. Bisacchi J. Med. Chem., 2015, 58 , 4874 —4882

Ziora ZM, Pham TDM, Blaskovich MAT. Quinolone antibiotics. Medchemcomm. 2019; 10(10):1719–39. https://doi.org/10.1039/c9md00120d PMID: 31803393

Patel, M. P. et al. Synergistic efects of functionally distinct substitutions in β-lactamase variants shed light on the evolution of bacterial drug resistance. J. Biol. Chem. 293, 17971–17984. https://doi.org/10.1074/jbc.RA118.003792 (2018).

Ur Rahman, S. et al. The growing genetic and functional diversity of extended spectrum beta-lactamases. Biomed. Res. Int. 2018, 9519718. https://doi.org/10.1155/2018/9519718 (2018).

Eiamphungporn, W., Schaduangrat, N., Malik, A. A. & Nantasenamat, C. Tackling the antibiotic resistance caused by class A β-lactamases through the use of β-lactamase inhibitory protein. Int. J. Mol. Sci. 19, 2222. https://doi.org/10.3390/ijms19082222 (2018)

Bush K and Jacoby G.A. Updated functional classification of beta-lactamases 2010 Mar;54(3):969-76. Antimicrob Agents Chemother.PMID: 19995920PMCID: PMC2825993 DOI: 10.1128/AAC.01009-09.

Hawkey, P. Molecular epidemiology of clinical significant antibiotic resistance genes. Br. J. Pharmacol. 153: 406-13 (2008)

Stadler, T. et al. Transmission of ESBL-producing Enterobacteriaceae and their mobile genetic elements—Identifcation of sources by whole genome sequencing: Study protocol for an observational study in Switzerland. BMJ Open 8, e021823. https://doi.org/10.1136/ bmjopen-2018-021823 (2018).

Shakya, P., Shrestha, D., Maharjan, E., Sharma, V. K. & Paudyal, R. ESBL production among E. coli and Klebsiella spp. causing urinary tract infection: A hospital based study. Open Microbiol. J. 11, 23–30. https://doi.org/10.2174/1874285801711010023 (2017).

McNulty, C. A. M. et al. CTX-M ESBL-producing Enterobacteriaceae: Estimated prevalence in adults in England in 2014. J. Antimicrob. Chemother. 73, 1368–1388. https://doi.org/10.1093/jac/dky007 (2018).

Teklu, D. S. et al. Extended-spectrum beta-lactamase production and multi-drug resistance among Enterobacteriaceae isolated in Addis Ababa, Ethiopia. Antimicrob. Resist. Infect. Control 8, 39. https://doi.org/10.1186/s13756-019-0488-4 (2019)

Rolain, J. M., Parola, P. And Cornaglia, G. (2010). New Delhi Metallo-Beta-Lactamase (NDM-1): Towards A New Pandemia? Clinical Microbiology and Infections. 16(12):1699-1701.

List of genera included in families - Enterobacteriaceae". "List of genera included in families - Enterobacteriaceae". List of Prokaryotic Names with Standing in Nomenclature. Retrieved 26 June 2016.

Don J. Brenner; Noel R. Krieg; James T. Staley (July 26, 2005) [1984 (Williams & Wilkins)]. George M. Garrity (ed.). The Gammaproteobacteria. Bergey's Manual of Systematic Bacteriology. Vol. 2B (2nd ed.). New York: Springer. p. 1108. ISBN 978-0-387-24144-9. British Library no. GBA561951.

Zipcodezoo site Enterobacteriales Archived 2014-04-27 at the Wayback Machine accessed 9 Mar 2013

NCBI Enterobacteriales accessed 9 Mar 2013

Taxonomicon Enterobacteriales accessed 9 Mar 2013

Adeolu, M; Alnajar, S; Naushad, S; S Gupta, R (December 2016). "Genome-based phylogeny and taxonomy of the 'Enterobacteriales': proposal for Enterobacterales ord. nov. divided into the families Enterobacteriaceae, Erwiniaceae fam. nov., Pectobacteriaceae fam. nov., Yersiniaceae fam. nov., Hafniaceae fam. nov., Morganellaceae fam. nov., and Budviciaceae fam. nov". International Journal of Systematic and Evolutionary Microbiology66(12):55755599 doi:10.1099/ijsem.0.001485. PMID27620848.

Ferreira da Silva, Miguel; Vaz-Moreira, Ivone; Gonzalez-Pajuelo, Maria; Nunes, Olga C.; Manaia, Célia M. (2007). "Antimicrobial resistance patterns in Enterobacteriaceae isolated from an urban wastewater treatment plant". FEMS Microbiology Ecology. Oxford University Press (OUP). 60 (1): 166–176. doi:10.1111/j.1574-6941.2006.00268.x. ISSN 0168-6496.

Wang, Zhiying; Hu, Huifeng; Zhu, Tongbo; Zheng, Jinshui; Gänzle, Michael G.; Simpson, David J. (31 August 2021). Rodríguez-Verdugo, Alejandra (ed.). Ecology and Function of the Transmissible Locus of Stress Tolerance in

Escherichia coli and Plant-Associated Enterobacteriaceae. Systems. American Society for Microbiology. 6 (4). doi:10.1128/msystems.00378-21. ISSN 2379-5077.

Edwards, P.R.; Ewing, W.H. (1972). Identification of Enterobacteriaceae. Burgess Publishing Company. ISBN 978-0-8087-0516-1.

Dorlands Medical Dictionary:Enterobacteriaceae. Archived from the original on 2009-08-28.

Feng P, Weagant S, Grant M (2002-09-01). Enumeration of Escherichia coli and the Coliform Bacteria". Bacteriological Analytical Manual (8th ed.). FDA/Center for Food Safety & Applied Nutrition. Archived from the original on 2009-05-19. Retrieved 2007-01-25.

Yu AC, Loo JF, Yu S, Kong SK, Chan TF (January 2014). "Monitoring bacterial growth using tunable resistive pulse sensing with a pore-based technique". Applied Microbiology and Biotechnology. 98 (2): 855–62. doi:10.1007/s00253-013-53779. PMID24287933. S2CID2956197.

Darnton NC, Turner L, Rojevsky S, Berg HC (March 2007). "On torque and tumbling in swimming Escherichia coli". Journal of Bacteriology. 189 (5): 1756–64. doi:10.1128/JB.01501-06. PMC 1855780. PMID 17189361.

Hudault S, Guignot J, Servin AL (July 2001). Escherichia coli strains colonising the gastrointestinal tract protect germfree mice against Salmonella typhimurium infection. Gut. 49 (1): 47–55. doi:10.1136/gut.49.1.47. PMC 1728375. PMID 11413110.

Reid G, Howard J, Gan BS (September 2001). Can bacterial interference prevent infection?. Trends in Microbiology. 9 (9):424–28. doi:10.1016/S0966842X(01)021321. PMID 11553454.

Mobley, Harry L. T.; Nataro, James P.; Kaper, James B. (February 2004). "Pathogenic Escherichia coli". Nature Reviews Microbiology. 2 (2): 123–140. doi:10.1038/nrmicro818. ISSN 1740-1534. PMID 15040260. S2CID 3343088

Figure 1: E coli under the Microscope -Gram Stain Techniques, Hanging Drop Methodwww.microscopemaster.com.

Evans Jr., Doyle J.; Dolores G. Evans. "Escherichia Coli". Medical Microbiology, 4th edition. The University of Texas Medical Branch at Galveston. Archived from the original on 2007-11-02. Retrieved 2007-12-02.

Heaton JC, Jones K (March 2008). "Microbial contamination of fruit and vegetables and the behaviour of enteropathogens in the phyllosphere: a review". J. Appl. Microbiol. 104 (3): 613–626. doi:10.1111/j.1365-2672.2007.03587.x. PMID 17927745. S2CID 2676938.

Thomas R. DeGregori (2007-08-17). "CGFI: Maddening Media Misinformation on Biotech and Industrial Agriculture". Archived from the original on 2007-10-13. Retrieved 2007-12-08.

Chalmers, R.M.; H. Aird, F.J. Bolton (2000). "Waterborne Escherichia coli O157". Society for Applied Microbiology Symposium Series. 88 (29): 124S–132S. doi:10.1111/j.1365-2672.2000.tb05340.x. PMID 10880187. S2CID 29924171.

Bach, S.J.; T.A. McAllister; D.M. Veira; V.P.J. Gannon; R.A. Holley (2002). "Transmission and control of Escherichia coli O157:H7". Canadian Journal of Animal Science. 82 (4): 475–490. doi:10.4141/A02-021.

Sabin Russell (October 13, 2006). "Spinach E. coli linked to cattle; Manure on pasture had same strain as bacteria in outbreak". San Francisco Chronicle. Retrieved 2007-12-02.

Wang L; Rothemund D; Reeves PR (May 2003). "Species-Wide Variation in the Escherichia coli Flagellin (H-Antigen) Gene". Journal of Bacteriology. 185 (9): 2396–2943. doi:10.1128/JB.185.9.2936-2943.2003. PMC 154406. PMID 12700273

Todar, K. "Pathogenic E. coli". Online Textbook of Bacteriology. University of Wisconsin–Madison Department of Bacteriology. Retrieved 2007-11-30

Croxen MA, Law RJ, Scholz R, Keeney KM, Wlodarska M, Finlay BB (2013). "Recent advances in understanding enteric pathogenic Escherichia coli". Clinical Microbiology Reviews. 26 (4): 822–80. doi:10.1128/CMR.00022-13. PMC 3811233. PMID 24092857.

Rendón, M. A.; et al. (2007). "Commensal and pathogenic Escherichia coli use a common pilus adherence factor for epithelial cell colonization". PNAS. 104 (25): 10637–10642. Bibcode:2007PNAS..10410637R. doi:10.1073/pnas.0704104104. PMC 1890562. PMID 17563352.

Martinez-Medina M, Garcia-Gil LJ (2014). "Escherichia coli in chronic inflammatory bowel diseases: An update on adherent invasive Escherichia

coli pathogenicity". World J Gastrointest Pathophysiol. 5 (3): 213–27. doi:10.4291/wjgp.v5.i3.213. PMC 4133521. PMID 25133024.

Szalanski A, Owens C, McKay T, Steelman C (2004). "Detection of Campylobacter and Escherichia coli O157:H7 from filth flies by polymerase chain reaction". Med Vet Entomol. 18 (3): 241–6. doi:10.1111/j.0269-283X.2004.00502.x. PMID 15347391. S2CID 15788942.

Sela S, Nestel D, Pinto R, Nemny-Lavy E, Bar-Joseph M (2005). "Mediterranean fruit fly as a potential vector of bacterial pathogens". Appl Environ Microbiol. 71 (7): 4052-6. Bibcode:2005ApEnM..71.4052S. doi:10.1128/AEM.71.7.4052-4056.2005. PMC 1169043. PMID 16000820.

Alam M, Zurek L (2004). "Association of Escherichia coli O157:H7 with houseflies on a cattle farm". Appl Environ Microbiol. 70 (12): 7578–80. Bibcode:2004ApEnM..70.7578A. doi:10.1128/AEM.70.12.7578-7580.2004. PMC 535191. PMID 15574966.

Heuvelink, A.E.; C. van Heerwaarden; J.T. Zwartkruis-Nahuis; R. van Oosterom; K. Edink; Y.T. van Duynhoven; E. de Boer (October 2002). "Escherichia coli O157 infection associated with a petting zoo". Epidemiology and Infection. 129 (2): 295–302. doi:10.1017/S095026880200732X. PMC 2869888. PMID 12403105.

Varma, J.K.; K.D. Greene; M.E. Reller; S.M. DeLong; J. Trottier; S.F. Nowicki; M. DiOrio; E.M. Koch; T.L. Bannerman; S.T. York; M.A. Lambert-Fair; J.G. Wells; P.S. Mead (November 26, 2003). "An outbreak of Escherichia coli O157 infection following exposure to a contaminated building". JAMA. 290 (20): 2709–2712. doi:10.1001/jama.290.20.2709. PMID 14645313

Institute of Medicine of the National Academies; Committee on the Review of the USDA E. coli O157:H7 Farm-to-Table Process Risk Assessment; Board on Health Promotion and Disease Prevention Food and Nutrition Board; Institute of Medicine of the National Academies (2002). Escherichia coli O157:H7 in Ground Beef: Review of a Draft Risk Assessment. Washington, D.C.: The National Academies Press. ISBN 978-0-309-08627-1.

Tauschek M, Gorrell R, Robins-Browne RM (2002). "Identification of a protein secretory pathway for the secretion of heat-labile enterotoxin by an enterotoxigenic strain of Escherichia coli". PNAS. 99 (10):706671.

Bibcode:2002PNAS...99.7066T. doi:10.1073/pnas.092152899. PMC 124529. PMID 12011463.

Wong CS, Jelacic S, Habeeb RL, et al. (29 June 2000). "The risk of the hemolytic-uremic syndrome after antibiotic treatment of Escherichia coli O157:H7 infections". N Engl J Med. 342 (26): 1930–6. doi:10.1056/NEJM200006293422601. PMC 3659814. PMID 10874060

Rolhion N, Darfeuille-Michaud A (2007). "Adherent-invasive Escherichia coli in inflammatory bowel disease". Inflamm. Bowel Dis. 13 (10): 1277–1283. doi:10.1002/ibd.20176. PMID 17476674. S2CID 9818154.

Baumgart M, Dogan B, Rishniw M, et al. (2007). "Culture independent analysis of ileal mucosa reveals a selective increase in invasive Escherichia coli of novel phylogeny relative to depletion of Clostridiales in Crohn's disease involving the ileum". ISME J. 1 (5): 403418 doi: 10.1038/ ismej. 2007.52.PMID 18043660.

Hand, T. W.; Dos Santos, L. M.; Bouladoux, N.; Molloy, M. J.; Pagán, A. J.; Pepper, M.; Maynard, C. L.; Elson CO III; Belkaid, Y. (30 August 2012). "Neurodevelopment: Low-flow blood-vessel pruning". Nature. 337 (6101): 1553–1556.

Nicolle LE (February 2008). "Uncomplicated urinary tract infection in adults including uncomplicated pyelonephritis". Urol. Clin. North Am. 35 (1): 1–12. doi:10.1016/j.ucl.2007.09.004. PMID 18061019.

Fig 2: E coli bacteria growing on mini-guts- blogs.bcm.edu.

Identified Virulence Factors of UPEC: Adherence, State Key Laboratory for Moleclular Virology and Genetic Engineering, Beijing. Retrieved July 2011

Justice S, Hunstad D, Seed P, Hultgren S (2006). "Filamentation by Escherichia coli subverts innate defenses during urinary tract infection". Proc Natl Acad Sci USA. 103 (52): 198849. Bibcode:2006PNAS..10319884J. doi:10.1073/pnas.0606329104. PMC 1750882.PMID17172451

Ehrlich G, Hu F, Shen K, Stoodley P, Post J (August 2005). "Bacterial plurality as a general mechanism driving persistence in chronic infections". Clin Orthop Relat Res (437): 20–4. doi:10.1097/00003086-200508000-00005. PMC 1351326. PMID 16056021.

Croxen, M A; Finlay, B B (2010). "Molecular mechanisms of Escherichia coli pathogenicity". Nature Reviews. Microbiology. 8 (1): 26–38. doi:10.1038/nrmicro2265. PMID 19966814. S2CID 6900440.

Balskus EP (2015). "Colibactin: understanding an elusive gut bacterial genotoxin". Natural Product Reports. 32 (11): 1534–40. doi:10.1039/c5np00091b. PMID 26390983.

Cuevas-Ramos G, Petit CR, Marcq I, Boury M, Oswald E, Nougayrède JP (2010). "Escherichia coli induces DNA damage in vivo and triggers genomic instability in mammalian cells". Proceedings of the National Academy of Sciences of the United States of America. 107 (25): 11537–11542. Bibcode:2010PNAS..10711537C. doi:10.1073/pnas.1001261107. PMC 2895108. PMID 20534522.

Secher T, Samba-Louaka A, Oswald E, Nougayrède JP (2013). "Escherichia coli producing colibactin triggers premature and transmissible senescence in mammalian cells". PLOS One. 8 (10): e77157. Bibcode:2013PLoSO...877157S. doi:10.1371/journal.pone.0077157. PMC 3792898. PMID 24116215.

Louis P, Hold GL, Flint HJ (2014). "The gut microbiota, bacterial metabolites and colorectal cancer". Nature Reviews. Microbiology. 12 (10): 661–72. doi:10.1038/nrmicro3344. PMID 25198138. S2CID 19619374.

Arthur, Janelle C.; et al. (5 October 2012). "Intestinal Inflammation Targets Cancer-Inducing Activity of the Microbiota. Science. 338 (6103): 120 123. Bibcode:2012 Sci...338..120A. doi:10.1126/science.1224820 PMC 3645302. PMID 22903521

Tonu N.S , Sufian M. A , Sarker S, Kamal M.M, Rahman M.H and Hossain M.M. 2011. PATHOLOGICAL STUDY ON COLIBACILLOSIS IN CHICKENS AND DETECTION OF ESCHERICHIA COLI BY PCR.Bangl. J. Vet. Med. (2011). 9(1): 17 – 25

Zander DS, Farver CF (2016). Pulmonary Pathology: A Volume in Foundations in Diagnostic Pathology Series. Elsevier Health Sciences. p. 169. ISBN 978-0-323-46119-1. Retrieved 14 January 2017.

Ryan, KJ; Ray, CG, eds. (2004). Sherris Medical Microbiology (4th ed.). McGraw Hill. ISBN 978-0-8385-8529-0.

Magill, S. S., Edwards, J. R., Bamberg, W., Beldavs, Z. G., Dumyati, G., Kainer, M. A., et al. (2014). Multistate point-prevalence survey of health care–associated infections. N. Engl. J. Med. 370, 1198–1208. doi: 10.1056/NEJMoa1306801

Riggs, PJ; Chelius MK; Iniguez AL; Kaeppler SM; Triplett EW (2001). "Enhanced maize productivity by inoculation with diazotrophic bacteria". Australian Journal of Plant Physiology. 29 (8): 829–836. doi:10.1071/PP01045.

Figure 3: Image of K pneumoniae on MacConkey agar from the Centers for Disease Control (CDC) and Prevention's Public Health Image Library (PHIL) with identification number #6689.

Ronning TG, Aas CG, Støen R, Bergh K, Afset JE, Holte MS, Radtke A. Investigation of an outbreak caused by antibiotic-susceptible Klebsiella oxytoca in a neonatal intensive care unit in Norway. Acta Paediatr. 2019 Jan;108(1):76-82.

Tsereteli M, Sidamonidze K, Tsereteli D, Malania L, Vashakidze E. Epidemiology Of Carbapenem-Resistant Klebsiella Pneumoniae In Intensive Care Units Of Multiprofile Hospitals In Tbilisi, Georgia. Georgian Med News. 2018 Jul-Aug;(280-281):164-168.

Esposito EP, Cervoni M, Bernardo M, Crivaro V, Cuccurullo S, Imperi F, Zarrilli R. Molecular Epidemiology and Virulence Profiles of Colistin-Resistant Klebsiella pneumoniae Blood Isolates From the Hospital Agency "Ospedale dei Colli," Naples, Italy. Front Microbiol. 2018;9:1463.

Walter J, Haller S, Quinten C, Kärki T, Zacher B, Eckmanns T, Abu Sin M, Plachouras D, Kinross P, Suetens C, Ecdc Pps Study Group Healthcare-associated pneumonia in acute care hospitals in European Union/European Economic Area countries: an analysis of data from a point prevalence survey, 2011 to 2012. Euro Surveill. 2018 Aug;23(32)

Richards, M. J., Edwards, J. R., Culver, D. H., and Gaynes, R. P. (2000). Nosocomial infections in combined medical-surgical intensive care units in the United States. Infect. Control Hosp. Epidemiol. 21, 510–515. doi: 10.1086/501795

Kalanuria, A. A., Zai, W., and Mirski, M. (2014). Ventilator-associated pneumonia in the ICU. Crit. Care 18:208. doi: 10.1186/cc13775

Selina, F., Talha, K. A., Islam, A., Hasan, Z., Hyder, M., and Selvapandian, S. (2014). Organisms associated with ventilator associated pneumonia (VAP)

in intensive care units (ICU). J. BSA 22, 72–77. doi: 10.3329/jbsa.v22i2.18146.

Mandell, G. L. (2005). Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. Philadelphia, PA: Elsevier.

Wang JL, Chen KY, Fang CT, Hsueh PR, Yang PC, Chang SC. 2005. Changing bacteriology of adult community-acquired lung abscess in Taiwan: Klebsiella pneumoniae versus anaerobes. Clin Infect Dis 40:915–922.

Lin YT, Jeng YY, Chen TL, Fung CP. 2010. Bacteremic community-acquired pneumonia due to Klebsiella pneumoniae: clinical and microbiological characteristics in Taiwan, 2001–2008. BMC Infect Dis 10:307.

Kang, C. I., Kim, S. H., Bang, J. W., Kim, H. B., Kim, N. J., Kim, E. C., et al. (2006). Community-acquired versus nosocomial Klebsiella pneumoniae Bacteremia: clinical features, treatment outcomes, and clinical implication of antimicrobial resistance. J. Korean Med. Sci. 21, 816–822. doi: 10.3346/jkms.2006.21.5.81.

Meatherall, B. L., Gregson, D., Ross, T., Pitout, J. D. D. and Laupland, K. B. (2009). Incidence risk factors, and outcomes of Klebsiella pneumoniae bacteremia. Am. J. Med. 122, 866–873. doi: 10.1016/j.amjmed.2009.03.034.

Schroll, C., Barken, K. B., Krogfelt, K. A., and Struve, C. (2010). Role of type 1 and type 3 fimbriae in Klebsiella pneumoniae biofilm formation. BMC Microbiol. 10:179. doi: 10.1186/1471-2180-10-179

Oana Mariana Cristea, Carmen Silvia Avramescu, Maria Balasoiu, F.D. Popescu, Florica Popescu, and M.O. Amzoiu (2017).Urinary tract infection with Klebsiella pneumoniae in Patients with Chronic Kidney Disease. Curr Health Sci J > v.43(2); PMC6284181.doi: 10.12865/CHSJ.43.02.06.

M. Vading, P. Nauclér, M. Kalin and C. G. Giske (2018). Invasive infection caused by Klebsiella pneumoniae is a disease affecting patients with high comorbidity and associated with high long-term mortality. doi: 10.1371/journal.pone.0195258.

Murthy V; Mahmoudi M; Rastogi N; Luk A; Phillips M; Kwon S; Nolan A (2015). Klebsiella pneumoniae meningitis associated with acute vasculitis and stroke. http://www.atsjournals.org/doi/pdf/10.1164/ajrccm-conference.2015.191.1_MeetingAbstracts.A1681. Am J Respir Crit Care Med 191(Abstract Issue):A1681. NIOSHTIC No.20048578.

Benjamin Kambiz Ghiam, Paul Israelsen, Angeline Wang, Seanna Grob and Mohammad Riazi Esfahani (2019). Klebsiella pneumoniae endogenous endophthalmitis presenting as orbital cellulitis. GMS Ophthalmol Cases.PMCID: PMC6734497;PMID: 31531276;9:Doc30. doi: 10.3205/oc000119.

Figure 4: Image from Chiu-Bin Hsaio reprinted with permission from McGraw- Hill Education 353.

Alexander Muacevic and John R Adler (2017). Klebsiella Pneumoniae Liver Abscess: a Case Report and Review of Literature. PMCID: PMC5298907;PMID: 28191374; doi: 10.7759/cureus.970.

Rossi B, Gasperini ML, Leflon-Guibout V, Gioanni A, de Lastours V, Rossi G, Dokmak S, Ronot M, Roux O, Nicolas-Chanoine MH, Fantin B, Lefort A. 2018. Hypervirulent Klebsiella pneumoniae in cryptogenic liver abscesses, Paris, France. Emerg Infect Dis 24:221–229.

Michelle K. Paczosa, Joan Mecsas (2016) Klebsiella pneumoniae: Going on the Offense with a Strong Defense. ASM Journals;Microbiology and Molecular Biology ReviewsVol. 80, No. 3. DOI: https://doi.org/10.1128/MMBR.00078-15.

Antoniadou A, Kontopidou F, Poulakou G, Koratzanis E, Galani I, Papadomichelakis E, Kopterides P, Souli M, Armaganidis A, Giamarellou H (April 2007). "Colistin-resistant isolates of Klebsiella pneumoniae emerging in intensive care unit patients: first report of a multiclonal cluster". The Journal of Antimicrobial Chemotherapy. 59 (4): 786–90. doi:10.1093/jac/dkl562. PMID 17307769.

Pearson MM, Sebaihia M, Churcher C, Quail MA, Seshasayee AS, Luscombe NM, et al. Complete genome sequence of uropathogenic Proteus mirabilis, a master of both adherence and motility. J Bacteriol. 2008;190:4027–37. [PMC free article] [PubMed] [Google Scholar] [Ref list]

Penner, J. L. (2005). “Genus XXIX. Proteus,” in Bergey's Manual of Systematic Bacteriology. The Proteobacteria: Part B, the Gammaproteobacteria, 2nd Edn., eds D. J. Brenner, N. R. Krieg, J. T. Staley and G. M. Garrity (Philadelphia, PA: Lippincott Williams & Wilkins), 745–753.

Drzewiecka D. Significance and roles of Proteus spp. bacteria in natural environments. Microb Ecol. 2016;72(4):741–58.

O'Hara CM, Brenner FW, Miller JM. Classification, identification, and clinical significance of Proteus, Providencia, and Morganella. Clin Microbiol Rev. 2000;13:534–546. [PMC free article] [PubMed] [Google Scholar] [Ref list]

Sabbuba NA, Mahenthiralingam E, Stickler DJ. Molecular epidemiology of Proteus mirabilis infections of the catheterized urinary tract. J Clin Microbiol. 2003;41(11):4961–5.

Wang S, Zhang Y, Zhang X, Li J. An evaluation of multidrug-resistant (MDR) bacteria in patients with urinary stone disease: data from a high-volume stone management center. World J Urol. 2020 Feb;38(2):425-432. [PubMed] [Reference list]

Potron A, Hocquet D, Triponney P, Plésiat P, Bertrand X, Valot B. Carbapenem-Susceptible OXA-23-Producing Proteus mirabilis in the French Community. Antimicrob Agents Chemother. 2019 Jun;63(6) [PMC free article] [PubMed] [Reference list]

O'Keefe LC, Koelle P, McGee Z, Dewberry LS, Wright C, Stallings JE, Gates E, Chittur K. Innovations in Worksite Diagnosis of Urinary Tract Infections and the Occupational Health Nurse. Workplace Health Saf. 2019 Jun;67(6):268-274. [PubMed] [Reference list]

Odoki M, Almustapha Aliero A, Tibyangye J, Nyabayo Maniga J, Wampande E, Drago Kato C, Agwu E, Bazira J. Prevalence of Bacterial Urinary Tract Infections and Associated Factors among Patients Attending Hospitals in Bushenyi District, Uganda. Int J Microbiol. 2019;2019:4246780. [PMC free article] [PubMed] [Reference list]

Rather PN. Swarmer cell differentiation in Proteus mirabilis. Environ Microbiol. 2005;7:1065–73. [PubMed] [Google Scholar] [Ref list]

Matthews SJ, Lancaster JW. Urinary tract infections in the elderly population. Am J Geriatr Pharmacother. 2011;9:286–309. [PubMed] [Google Scholar] [Ref list]

Papazafiropoulou A, Daniil I, Sotiropoulos A, Balampani E, Kokolaki A, Bousboulas S, Konstantopoulou S, Skliros E, Petropoulou D, Pappas S. Prevalence of asymptomatic bacteriuria in type 2 diabetic subjects with and without microalbuminuria. BMC Res Notes. 2010;3:169. [PMC free article] [PubMed] [Google Scholar] [Ref list]

Figure 5: Colonies of Proteus mirabilis bacteria grown on XLD agar plate.www.alamy.com

Janda JMA, Abbott SL. The Enterobacteria. 2 ed. ASM Press; Washington, D.C.: 2006. [Google Scholar] [Ref list]

Meini S, Tascini C, Cei M, Sozio E, Rossolini GM. AmpC β-lactamase-producing Enterobacterales: what a clinician should know. Infection. 2019 Jun;47(3):363-375. [PubMed] [Reference list]

Gonzales, Gus. Proteus Infections. eMedicine from WebMD. Last edited 2 March 2006. Accessed Nov. 30, 2008.http://www.emedicine.com/med/TOPIC1929.HTM

Mathur S, Sabbuba NA, Suller MT, Stickler DJ, Feneley RC. Genotyping of urinary and fecal Proteus mirabilis isolates from individuals with long-term urinary catheters. Eur J Clin Microbiol Infect Dis. 2005;24:643–644. [PubMed] [Google Scholar] [Ref list]

Stickler DJ. Bacterial biofilms in patients with indwelling urinary catheters. Nat Clin Pract Urol. 2008;5:598–608. [PubMed] [Google Scholar]

Mobley HLT. 2001. Urease. In Mobley HLT, Mendz GL, Hazell SL (ed), Helicobacter pylori: physiology and genetics doi:NBK2417. ASM Press, Washington, DC).

Munns J, Amawi F. 2010. A large urinary bladder stone: an unusual cause of rectal prolapse. Arch Dis Child 95:1026.)

Chew R, Thomas S, Mantha ML, Killen JP, Cho Y, Baer RA. 2012. Large urate cystolith associated with Proteus urinary tract infection. Kidney Int 81:802.

Torzewska A, Budzyńska A, Białczak-Kokot M, Różalski A. 2014. In vitro studies of epithelium-associated crystallization caused by uropathogens during urinary calculi development. Microb Pathog 71–72C:25–31

Figure 6: Li X, Zhao H, Lockatell CV, Drachenberg CB, Johnson DE, Mobley HLT. 2002. Visualization of Proteus mirabilis within the matrix of urease-induced bladder stonesduring experimental urinary tract infection. Infect Immun 70:389–394.). Figure 6.

Howery KE, Clemmer KM, Şimşek E, Kim M, Rather PN (August 2015). Armitage JP (ed.). "Regulation of the Min Cell Division Inhibition Complex by the Rcs Phosphorelay in Proteus mirabilis". Journal of Bacteriology. 197 (15): 2499–2507. doi:10.1128/JB.00094-15. PMC 4518839. PMID 25986901.

Morgenstein RM, Szostek B, Rather PN (September 2010). "Regulation of gene expression during swarmer cell differentiation in Proteus mirabilis". FEMS Microbiology Reviews. 34 (5): 753–763. doi:10.1111/j.1574-6976.2010.00229.x. PMID 20497230.

Bailey & Scott's Diagnostic Microbiology. Editors: Bettey A. Forbes, Daniel F. Sahm & Alice S. Weissfeld, 12th ed 2007, Publisher Elsevier.

Jones BV, Young R, Mahenthiralingam E, Stickler DJ. Ultrastructure of Proteus mirabilis swarmer cell rafts and role of swarming in catheter-associated urinary tract infection. Infect Immun. 2004;72:3941–3950. [PMC free article] [PubMed] [Google Scholar] [Ref list]

Sabbuba N, Hughes G, Stickler DJ. The migration of Proteus mirabilis and other urinary tract pathogens over Foley catheters. BJU Int. 2002;89:55–60. [PubMed] [Google Scholar] [Ref list]

Figure 7: swarming phenomenon. Jessica N. Schaffer, Melanie M. Pearson. 2015.Proteus mirabilis and Urinary Tract Infections: ASM Journals/Microbiology Spectrum/Vol. 3, No. 5. DOI: https://doi.org/10.1128/microbiolspec.UTI-0017-2013

Flemming, H. C., and Wingender, J. (2010). The biofilm matrix. Nat. Rev. Microbiol. 8, 623–633. doi: 10.1038/nrmicro2415

Harshey, R.M. (2003). Bacterial motility on a surface: many ways to a common goal. Annu. Rev. Microbiol. 57, 249–273. doi: 10.1146/annurev.micro.57.030502.091014

Jones, G. L., Russell, A. D., Caliskan, Z., and Stickler, D. J. (2005). A strategy for the control of catheter blockage by crystalline Proteus mirabilis biofilm using the antibacterial agent triclosan. Eur. Urol. 48, 838–845. doi: 10.1016/j.eururo.2005.07.004

Fraser, G. M., Claret, L., Furness, R., Gupta, S., and Hughes, C. (2002). Swarming-coupled expression of the Proteus mirabilis hpmBA haemolysin operon. Microbiology (Reading, England) 148, 2191–2201. doi: 10.1099/00221287-148-7-2191

Liaw, S. J., Lai, H. C., Ho, S. W., Luh, K. T., and Wang, W. B. (2003). Role of RsmA in the regulation of swarming motility and virulence factor expression in Proteus mirabilis. J. Med. Microbiol. 52, 19–28. doi: 10.1099/jmm.0.05024-0

Donlan, R. M. (2002). Biofilms: microbial life on surfaces. Emerg. Infect. Dis. 8, 881–890. doi: 10.3201/eid0809.020063

Downer, A., Morris, N., Feast, W. J., and Stickler, D. (2003). Polymer surface properties and their effect on the adhesion of Proteus mirabilis. Proc. Inst. Mech. Eng. H 217, 279–289. doi: 10.1243/095441103322060730

Jacobsen, S., and Shirtliff, M. (2011). Proteus mirabilis biofilms and catheter-associated urinary infections. Virulence 2, 460–465. doi: 10.4161/viru.2.5.17783

Bichler, K. H., Eipper, E., Naber, K., Braun, V., Zimmermann, R., and Lahme, S. (2002). Urinary infection stones. Int. J. Antimicrob. Agents 19, 488–498. doi: 10.1016/S0924-8579(02)00088-2

Burne, R. A., and Chen, Y. Y. (2000). Bacterial ureases in infectious diseases. Microbes. Infect. 2, 533–542. doi: 10.1016/S1286-4579(00)00312-9

Figure 8: Reham Wasfi, Samira M. Hamed, Mai A. Amer and Lamiaa Ismail Fahmy. 14 August 2020: Proteus mirabilis Biofilm: Development and Therapeutic Strategies. Front. Cell. Infect. Microbiol.. DOI:https://doi.org/10.3389/fcimb.2020.00414

Hospenthal MK, Costa TRD, Waksman G. A comprehensive guide to pilus biogenesis in Gram-negative bacteria. Nat Rev Microbiol. 2017;15:365–379.

Kuan L, Schaffer JN, Zouzias CD, Pearson MM. Characterization of 17 chaperone-usher fimbriae encoded by Proteus mirabilis reveals strong conservation. J Med Microbiol. 2014;63:911–922).

Snyder JA, Haugen BJ, Lockatell CV, Maroncle N, Hagan EC, Johnson DE, Welch RA, Mobley HL. Coordinate expression of fimbriae in uropathogenic Escherichia coli. Infect Immun. 2005;73:7588–7596.

Welch RA, Burland V, Plunkett G, 3rd, Redford P, Roesch P, Rasko D, Buckles EL, Liou SR, Boutin A, Hackett J, Stroud D, Mayhew GF, Rose DJ, Zhou S, Schwartz DC, Perna NT, Mobley HL, Donnenberg MS, Blattner FR. Extensive mosaic structure revealed by the complete genome sequence of uropathogenic Escherichia coli. Proc Natl Acad Sci U S A. 2002;99:17020–17024.).

Schaffer JN, Pearson MM. Proteus mirabilis and Urinary Tract Infections. Microbiol Spectr. 2015;3

Norsworthy AN, Pearson MM. From Catheter to Kidney Stone: The Uropathogenic Lifestyle of Proteus mirabilis. Trends Microbiol. 2016 doi: 10.1016/j.tim.2016.11.015.

Rocha SPD, Pelayo JS, Elias WP. Fimbriae of uropathogenic Proteus mirabilis. FEMS Immunology & Medical Microbiology. 2007;51:1–7.

Zunino P, Sosa V, Schlapp G, Allen AG, Preston A, Maskell DJ. Mannose-resistant Proteus-like and P. mirabilis fimbriae have specific and additive roles in P. mirabilis urinary tract infections. FEMS Immunology & Medical Microbiology. 2007;51:125–133.

Li X, Mobley HLT. Vaccines for Proteus mirabilis in urinary tract infection. International Journal of Antimicrobial Agents. 2002;19:461–465.

Pellegrino R, Galvalisi U, Scavone P, Sosa V, Zunino P. Evaluation of Proteus mirabilis structural fimbrial proteins as antigens against urinary tract infections. FEMS Immunology & Medical Microbiology. 2003;36:103–110.

Li X, Lockatell CV, Johnson DE, Lane MC, Warren JW, Mobley HLT. Development of an Intranasal Vaccine To Prevent Urinary Tract Infection by Proteus mirabilis. Infect Immun. 2004;72:66–75

Scavone P, Sosa V, Pellegrino R, Galvalisi U, Zunino P. Mucosal vaccination of mice with recombinant Proteus mirabilis structural fimbrial proteins. Microbes and Infection. 2004;6:853–860.

Cestari SE, Ludovico MS, Martins FH, da Rocha SP, Elias WP, Pelayo JS. Molecular detection of HpmA and HlyA hemolysin of uropathogenic Proteus mirabilis. Curr Microbiol. 2013;67:703–707.

Coker C, Poore CA, Li X, Mobley HLT. Pathogenesis of Proteus mirabilis urinary tract infection. Microbes and Infection. 2000;2:1497–1505).

Jamil, R. T., Foris, L. A., and Snowden, J. (2020). “Proteus mirabilis infections,” in StatPearls. (Treasure Island, FL: StatPearls Publishing). Available online at: https://www.ncbi.nlm.nih.gov/books/NBK442017/PubMed Abstract | Google Scholar

Jones, S. M., Yerly, J., Hu, Y., Ceri, H., and Martinuzzi, R. (2007). Structure of Proteus mirabilis biofilms grown in artificial urine and standard laboratory media. FEMS Microbiol. Lett. 268, 16–21. doi: 10.1111/j.1574-6968.2006.00587.

Chen, C. Y., Chen, Y. H., Lu, P. L., Lin, W. R., Chen, T. C., and Lin, C. Y. (2012). Proteus mirabilis urinary tract infection and bacteremia: risk factors, clinical presentation, and outcomes. J. Microbiol. Immunol. Infect. 45, 228–236. doi: 10.1016/j.jmii.2011.11.007

Vaidyanathan, S., Soni, B. M., Hughes, P. L., Singh, G., and Oo, T. (2010). Severe ventral erosion of penis caused by indwelling urethral catheter and inflation of Foley balloon in urethra-need to create list of "never events in spinal cord injury" in order to prevent these complications from happening in paraplegic and tetraplegic patients. Adv. Urol. 2010:461539. doi: 10.1155/2010/461539

Jacobsen, S. M., Stickler, D. J., Mobley, H. L., and Shirtliff, M. E. (2008). Complicated catheter-associated urinary tract infections due to Escherichia coli and Proteus mirabilis. Clin. Microbiol. Rev. 21, 26–59. doi: 10.1128/CMR.00019-07

Nicolle, L.E. (2014). Catheter associated urinary tract infections. Antimicrob. Resist. Infect. Control. 3:23. doi: 10.1186/2047-2994-3-23

Karlowsky JA, Lagacé-Wiens PR, Simner PJ, DeCorby MR, Adam HJ, Walkty A, Hoban DJ, Zhanel GG. Antimicrobial resistance in urinary tract pathogens in Canada from 2007 to 2009: CANWARD surveillance study. Antimicrob Agents Chemother. 2011;55:3169–3175

Nielubowicz GR, Mobley HLT. Host-pathogen interactions in urinary tract infection. Nat Rev Urol. 2010;7:430–441

Nicolle LE. Catheter-related urinary tract infection. Drugs Aging. 2005;22:627–639

Hung EW, Darouiche RO, Trautner BW. Proteus bacteriuria is associated with significant morbidity in spinal cord injury. Spinal Cord. 2007;45:616–620

Adams-Sapper S, Sergeevna-Selezneva J, Tartof S, Raphael E, Diep BA, Perdreau-Remington F, Riley LW. Globally dispersed mobile drug-resistance genes in gram-negative bacterial isolates from patients with bloodstream infections in a US urban general hospital. J Med Microbiol. 2012;61:968–974.

Mylotte JM. Nursing home-acquired bloodstream infection. Infect Control Hosp Epidemiol. 2005;26:833–837

Sader HS, Flamm RK, Jones RN. Frequency of occurrence and antimicrobial susceptibility of Gram-negative bacteremia isolates in patients with urinary

tract infection: results from United States and European hospitals (2009-2011). J Chemother. 2014;26:133–138.

Lubart E, Segal R, Haimov E, Dan M, Baumoehl Y, Leibovitz A. Bacteremia in a multilevel geriatric hospital. J Am Med Dir Assoc. 2011;12:204–207.

Tonki M, Mohar B, Sisko-Kraljevi K, Mesko-Meglic K, Goić-Barisi I, Novak A, Kovaci A, Punda-Poli V. High prevalence and molecular characterization of extended-spectrum β-lactamase-producing Proteus mirabilis strains in southern Croatia. J Med Microbiol 2010;59: 1185-1190).

Mokracka J, Gruszczyńska B, Kaznowski A. Integrons, β-lactamase and qnr genes in multidrug resistant clinical isolates of Proteus mirabilis and P. vulgaris. APMIS 2012;120: 950-958

Wenren LM, Sullivan NL, Cardarelli L, Septer AN, Gibbs KA. Two Independent Pathways for Self-Recognition in Proteus mirabilis Are Linked by Type VI-Dependent Export. mBio 2013;4: e00374-00313.

Rashid T, Ebringer A. Rheumatoid arthritis is linked to Proteus--the evidence. Clin Rheumatol. 2007;26:1036–1043.

Spellberg B, Blaser M, Guidos RJ, Boucher HW, Bradley JS, Eisenstein BI, et al.Infectious Diseases Society of America (IDSA) Combating antimicrobial resistance: policy recommendations to save lives. Clin Infect Dis 2011. May;52(Suppl 5):S397-S428

Lobanovska M, Pilla G. Penicillin's Discovery and Antibiotic Resistance: Lessons for the Future? Yale J Biol Med 2017. Mar;90(1):135-145.

Murray PR, Rosenthal KS MpM. Medical Microbiology 5th ed. Philadelphia, Pennsylvania USA; 2005.

Paterson DL. Resistance in gram-negative Bacteria: Enterobacteriaceae. Am J Med. 2006;119(6):20–8.

Tzelepi E, Giakkoupi P, Sofianou D, Loukova V. Kemeroglou a, Tsakris a. Detection of extended-spectrum beta-lactamases in clinical isolates of Enterobacter cloacae and Enterobacter aerogenes. J Clin Microbiol. 2000; 38(2):542–6

Paterson DL, Bonomo RA. Extended-Spectrum Beta-lactamases : a clinical update. Clin Microbiol Rev. 2005;18(4):657–86.

Pitout JDLK. Extended-spectrum β-lactamase-producing Enterobacteriaceae: an emerging public-health concern. Lancet Infect Dis. 2008;8(3):159–66.

Bush K, Fisher JF. Epidemiological expansion , structural studies and clinical challenges of new β-lactamases from gram-negative Bacteria. Annu Rev Microbilogy. 2011;65:455–78

Schwaber MJ, Navon-venezia S, Schwartz D, Schwaber MJ, Navon-venezia S, Schwartz D, et al. High levels of antimicrobial Coresistance among extended-Spectrum-beta-lactamase-producing Enterobacteriaceae. Antimicrob Agents Chemother. 2005;49(5):2137–9.

Chandel DS, Johnson JA, Chaudhry R, Sharma N, Shinkre N, Parida S, et al. Extended-spectrum b -lactamase-producing gram-negative bacteria causing neonatal sepsis in India in rural and urban settings. J Med Microbiol. 2011:500–7.

Bader MS, Loeb M, Brooks AA — An update on the management of urinary tract infections in the era of antimicrobial resistance. Postgrad Med 2017; 129(2): 242-58.

Livermore DM, Woodford N. The beta-lactamase threat in Enterobacteriaceae, Pseudomonas and Acinetobacter. Trends Microbiol 2006;14(9):413–20, http:// dx.doi.org/10.1016/j.tim.2006.07.008. Epub 2006 Jul 31].

Burke L, Humphreys H, Fitzgerald-Hughes D. The revolving door between hospital and community: extended-spectrum beta-lactamase-producing Escherichia coli in Dublin. J Hosp Infect 2012;81(3):192–8, http://dx.doi.org/ 10.1016/j.jhin.2012.04.021.

Cantón R, Coque TM. The CTX-M beta-lactamase pandemic. Curr Opin Microbiol 2006;9(5):466–75. http://dx.doi.org/10.1016/j.mib.2006.08.011. Epub 2006 Aug 30.

Coque TM, Baquero F, Canton R. Increasing prevalence of ESBL-producing Enterobacteriaceae in Europe. Euro Surveill 2008;13(47).

Stuart RL, Kotsanas D, Webb B, Vandergraaf S, Gillespie EE, Hogg GG, et al. Prevalence of antimicrobial-resistant organisms in residential aged care facilities. Med J Aust 2011;195(9):530–3.

Valenza G, Nickel S, Pfeifer Y, Eller C, Krupa E, Lehner-Reindl V, et al. Extendedspectrum--lactamase-producing Escherichia coli as intestinal colonizers in the German community. Antimicrob Agents Chemother 2014;58(2):1228–30, http://dx.doi.org/10.1128/AAC.01993-13.

Subha A, Ananthan S. Extended spectrum β-lactamase (ESBL) mediated resistance to third generation cephalosporins among Klebsiella pneumoniae in Chennai. Indian J Med Microbiol. 2002;20(2):92–95.

Johann, D.D. Pitout Kevin, B. Laupland. Extended Spectrum β- Lactamase-Producing Enterobacteriaceae: An emerging public-health concern. Lancet Infect.Dis.8:159-66 (2008).

David, L. Paterson, Maximizing Therapeutic Success in an Era of Increasing Antibiotic Drug Resistance (2007).

Luzzaro, F. Mezzatesta, M. Mugnaioli, C. Perilli, M. Stefani, S. Amicosante, G. et al., Trends in Production of Extended-spectrum ß-Lactamases among Enterobacteriaceae of Medical Interest:Report of the Second Italian Nationwide Survey.Journalof Clinical Microbiology, 44:1659- 1664 (2006).

Song, W. Kim, J. Bae, I.K. Jeong, S.H. Seo, Y.H. Shin, J.H. et al.,Chromosome-Encoded AmpC and CTXM Extended-Spectrum ß-Lactamases in Clinical Isolates of Proteus Mirabilis from Korea. Antimicrobial Agents and Chemotherapy, 55:1414-1419 (2011).

Figure 9: image of drug resistant and non-drug bacteria fromwww.researchgate.net.

Center for Disease Control and Prevention Antibiotic resistance threat in the United State 2019. https://www.cdc.gov/drugresistance/pdf/threats-reports/2019-ar-threats-report-508.pdf.

Pranita D Tamma, Samuel L Aitken, Robert A Bonono, Amy J Mathers, David Van Duin, Cornelius J Clancy. Infectious Diseases Society of America 2022. Guidance On The Treatment Of Extended Spectrum ß-Lactamase Prouding Enterobacterales (ESBL-E), Carbapenem- Resistant Enterobacterales (CRE) and Pseudomonas Aeruginosa With Difficult-To-Treat Resistance (DTR-P.Aeruginosa). Clinical Infectious Diseases, Volume 75, Issue 2. 15 July 2022: https://doi.org/10.1093/cid/ciac268.

Mandell, G.L., 2005, Uptake, transport, delivery, and intracellular activity of antimicrobial agents. Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy 25(12P2), 130S–133S. doi: 10.1592/phco.2005.25.12part2.130S

Shahcheraghi, F., Nobari, S., Rahmati, G.F., Nasiri, S., Owlia, P., Nikbin, V.S., and Imani Fooladi, A.A., 2013, First report of New Delhi metallo-beta-

lactamase-1-producing Klebsiella pneumoniae in Iran. Microbial Drug Resistance 19(1), 30–36. doi: 10.1089/ mdr.2012.0078

Piddock, L.J., 1999, Mechanisms of fluoroquinolone resistance: An update 1994–1998. Drugs 58(2), 11–18. doi: 10.2165/00003495-199958002-00003

Soussy, C.J., Wolfson, J.S., Ng, E.Y., and Hooper, D.C., 1993, Limitations of plasmid complementation test for determination of quinolone resistance due to changes in the gyrase A protein and identification of conditional quinolone resistance locus. Antimicrobial Agents and Chemotherapy 37(12), 2588–2592. doi: 10.1128/AAC.37.12.2588

Garau, J., Mariona, X., Rodríguez-Carballeira, M., Josep Ramón, G., Ignacio, C., Dolors, V., Teresa, L., and Ruíz-Bremón, A., 1999, Emergence and dissemination of quinolone-resistant Escherichia coli in the community. Antimicrobial Agents and Chemotherapy 43(11), 2736–2741.

Van Doorslaer, X., Dewulf, J., Van Langenhove, H., and Demeestere, K., 2014, Fluoroquinolone antibiotics: An emerging class of environmental micropollutants. Science of the Total Environment 500, 250–269.

Briales, A., Rodríguez-Martínez, J.M., Velasco, C., de Alba, P.D., Rodriguez-Bano, J., Martínez-Martínez, L., and Pascual, A., 2012, Prevalence of plasmid-mediated quinolone resistance determinants qnr and aac(6′)-Ib-cr in Escherichia coli and Klebsiella pneumoniae producing extended-spectrum β-lactamases in Spain. International Journal of Antimicrobial Agents 39(5), 431–434. doi: 10.1016/j.ijantimicag.2011.12.009

Alikhani, M.Y., Hashemi, S.H., Aslani, M.M., and Farajnia, S., 2013, Prevalence and antibiotic resistance patterns of diarrhoeagenic Escherichia coli isolated from adolescents and adults in Hamedan, Western Iran. Iranian Journal of Microbiology 5(1), 42.

Strahilevitz, J., Jacoby, G.A., Hooper, D.C., and Robicsek, A., 2009, Plasmid-mediated quinolone resistance: A multifaceted threat. Clinical Microbiology Reviews 22(4), 664–689. doi: 10.1128/CMR.00016-09

Hooper, D.C. and Jacoby, G.A., 2015, Mechanisms of drug resistance: Quinolone resistance. Annals of the New York Academy of Sciences 1354(1), 12–31. doi: 10.1111/nyas.12830.

Hernández, A., Sanchez, M.B., and Martínez, J.L., 2011, Quinolone resistance: Much more than predicted. Frontiers in Microbiology 2, 22. doi: 10.3389/fmicb.2011.00022

Jacoby, G.A., 2005, Mechanisms of resistance to quinolones. Clinical Infectious Diseases 41 (Supplement_2), S120–S126. doi: 10.1086/428052.

Oteo J, Campos J, Lázaro E, et al. Increased amoxicillin–clavulanic acid resistance in Escherichia coli blood isolates, Spain. Emerg. Infect. Dis. 2008;14(8):1259.

Ni Q, Tian Y, Zhang L, et al. Prevalence and quinolone resistance of fecal carriage of extended-spectrum β-lactamase-producing Escherichia coli in 6 communities and 2 physical examination center populations in Shanghai, China. Diagn. Microbiol. Infect. Dis. 2016;86(4):428–433.

Martı´nez-Martı´nez L., Pascual A., and Jacoby G.A., Quinolone resistance from a transferable plasmid. Lancet, 1998. 351(9105): p. 797–9. https://doi.org/10.1016/S0140-6736(97)07322-4 PMID: 9519952

Nordmann P. and Poirel L., Emergence of plasmid-mediated resistance to quinolones in Enterobacteriaceae. J Antimicrob Chemother, 2005. 56(3): p. 463–9. https://doi.org/10.1093/jac/dki245 PMID:16020539

Yanat B, Machuca J, Diaz-De-Alba P, et al. Characterization of plasmid-mediated quinolone resistance determinants in high-level quinolone resistant Enterobacteriaceae isolates from the community: first report of qnrD Gene in algeria. Microb Drug Resist. 2017;23(1):90–97.

Mansouri S, Abbasi S. Prevalence of multiple drug resistant clinical isolates of extended-spectrum beta-lactamase producing Enterobacteriaceae in Southeast Iran. Iran J Med Sci. 2015;35(2):101–108.

García-Fulgueiras V, Bado I, Mota MI, et al. Extended-spectrum β-lactamases and plasmid-mediated quinolone resistance in enterobacterial clinical isolates in the paediatric hospital of Uruguay. J Antimicrob Chemother. 2011;66(8):1725–1729.

Rodríguez-Martínez JM, Cano ME, Velasco C, Martínez-Martínez L, Pascual Á. Plasmid-mediated quinolone resistance: an update. J Infect Chemother. 2011;17(2):149-182.

Thu D M Pham, Zyta M Ziora, Mark A T Blaskovich. Quinolone antibiotics. MedChemComm. 2019;10:1719-1739.PMID: 31803393. DOI: 10.1039/c9md00120d.

Emmerson AM. The quinolones: Decades of development and use. The Journal of Antimicrobial Chemotherapy. 2003;51(90001):13-20. PMID: 12702699DOI: 10.1093/jac/dkg208.

Zhanel GG, Fontaine S, Adam H, Schurek K, Mayer M, Noreddin AM, Gin AS, Rubinstein E, Hoban DJ (2006). "A Review of New Fluoroquinolones : Focus on their Use in Respiratory Tract Infections". Treat Respir Med. 5 (6): 437–65. doi:10.2165/00151829-200605060-00009. PMID 17154673. S2CID 26955572.

Paterson, D.L. Mulazimoglu, L. Casellas, J.M., et al. Epidemiology of ciprofloxacin resistance and its relationship to extended-spectrum beta-lactamase production in Klebsiella pneumoniae isolates causing bacteremia. Clin Infect Dis. 30: 473-478 (2000)

Thenmozhi S, Moorthy K, Sureshkumar B. T, Suresh M. Antibiotic Resistance Mechanism of ESBL Producing Enterobacteriaceae in Clinical Field: A Review. Int. J. Pure App. Biosci. 2 (3): 207-226 (2014).

Figure 10: Site of antibiotic action courtesy- lumen learning

Ambler class A beta-lactamases: TEM and SHV. Beta-Lactamase DataBase BLDB

Sanders CC, Sanders WE (June 1979). "Emergence of resistance to cefamandole: possible role of cefoxitin-inducible beta-lactamases". Antimicrobial Agents and Chemotherapy. 15 (6): 792–797. doi:10.1128/AAC.15.6.792. PMC 352760. PMID 314270

Symanzik C, Hillenbrand J, Stasielowicz L, Greie JC, Friedrich AW, Pulz M, et al. (December 2021). "Novel insights into pivotal risk factors for rectal carriage of extended-spectrum-β-lactamase-producing enterobacterales within the general population in Lower Saxony, Germany". Journal of Applied Microbiology. 132 (4): 3256–3264. doi:10.1111/jam.15399. PMID 34856042. S2CID 244854840

Nicolas-Chanoine MH, Gruson C, Bialek-Davenet S, Bertrand X, Thomas-Jean F, Bert F, et al. (March 2013). "10-Fold increase (2006-11) in the rate of healthy subjects with extended-spectrum β-lactamase-producing Escherichia coli faecal carriage in a Parisian check-up centre". The Journal of Antimicrobial Chemotherapy. 68 (3): 562–568. doi:10.1093/jac/dks429. PMID 23143897.

Kader AA, Kamath KA (2009). "Faecal carriage of extended-spectrum beta-lactamase-producing bacteria in the community". Eastern Mediterranean Health Journal. 15 (6): 1365–1370. PMID 20218126

Valverde A, Grill F, Coque TM, Pintado V, Baquero F, Cantón R, Cobo J (August 2008). "High rate of intestinal colonization with extended-spectrum-beta-lactamase-producing organisms in household contacts of infected community patients". Journal of Clinical Microbiology. 46 (8): 2796–2799. doi:10.1128/JCM.01008-08. PMC 2519510. PMID 18562591

Emery CL, Weymouth LA August 1997. "Detection and clinical significance of extended-spectrum beta-lactamases in a tertiary-care medical center". Journal of Clinical Microbiology. 35 (8): 2061–2067. doi:10.1128/JCM.35.8.2061-2067.1997. PMC 229903. PMID 9230382.

Rupp M. E. and P. D. Fey, "Extended spectrum β-lactamase (ESBL)-producing Enterobacteriaceae: considerations for diagnosis, prevention and drug treatment," Drugs, 63(4): 353–365 (2003).

Rishi H, P.Dhillon and John Clark. ESBLs: A Clear and Danger? Critical Care Research and Practice. 2012.

Cooksey R, Swenson J, Clark N, Gay E, Thornsberry C (May 1990). "Patterns and mechanisms of beta-lactam resistance among isolates of Escherichia coli from hospitals in the United States". Antimicrobial Agents and Chemotherapy. 34 (5): 739–45. doi:10.1128/AAC.34.5.739. PMC 171683. PMID 2193616.

Paterson DL, Hujer KM, Hujer AM, Yeiser B, Bonomo MD, Rice LB, Bonomo RA (November 2003). "Extended-spectrum beta-lactamases in Klebsiella pneumoniae bloodstream isolates from seven countries: dominance and widespread prevalence of SHV- and CTX-M-type beta-lactamases". Antimicrobial Agents and Chemotherapy. 47 (11): 3554–60. doi:10.1128/AAC.47.11.3554-3560.2003. PMC 253771. PMID 14576117.

Bradford PA (October 2001). "Extended-spectrum beta-lactamases in the 21st century: characterization, epidemiology, and detection of this important resistance threat". Clinical Microbiology Reviews. 14 (4): 933–51, table of contents. doi:10.1128/CMR.14.4.933-951.2001. PMC 89009. PMID 11585791.

Jacoby GA, Munoz-Price LS (January 2005). "The new beta-lactamases". The New England Journal of Medicine. 352 (4): 380–91. doi:10.1056/NEJMra041359. PMID 15673804.

Ruiz J (2018). Etymologia: TEM. Emerging Infectious Diseases.24 (4): 709. doi:10.3201/eid2404.et2404.

Liakopoulos A, Mevius D, Ceccarelli D (5 September 2016). A Review of SHV Extended-Spectrum β-Lactamases: Neglected Yet Ubiquitous. Frontiers in Microbiology. 7:1374. doi:10.3389/fmicb.2016.01374. PMC 5011133. PMID 27656166.

Cantón R, González-Alba JM, Galán JC (2012). "CTX-M Enzymes: Origin and Diffusion". Frontiers in Microbiology. 3: 110. doi:10.3389/fmicb.2012.00110. ISSN 1664-302X. PMC 3316993. PMID 22485109.

Ramadan AA, Abdelaziz NA, Amin MA, Aziz RK (March 2019). "Novel blaCTX-M variants and genotype-phenotype correlations among clinical isolates of extended spectrum beta lactamase-producing Escherichia coli". Scientific Reports. 9 (1): 4224. Bibcode:2019NatSR...9.4224R. doi:10.1038/s41598-019-39730-0. PMC 6414621. PMID 30862858. S2CID 75136447.

Woodford N, Ward E, Kaufmann ME, et al. "Molecular characterisation of Escherichia coli isolates producing CTX-M-15 extended-spectrum β-lactamase (ESBL) in the United Kingdom" (PDF). Health Protection Agency. Archived from the original (PDF) on 15 June 2007. Retrieved 19 November 2006.

Hudson CM, Bent ZW, Meagher RJ, Williams KP (7 June 2014). "Resistance determinants and mobile genetic elements of an NDM-1-encoding Klebsiella pneumoniae strain". PLOS ONE. 9 (6): e99209. Bibcode:2014PLoSO...999209H. doi:10.1371/journal.pone.0099209. PMC 4048246. PMID 24905728.

Drlica K.; Hiasa H.; Kerns R.; Malik M.; Mustaev A.; Zhao X. (2009) Quinolones: Action and resistance updated. Curr. Top. Med. Chem. 9, 981–998. [Europe PMC free article] [Abstract] [Google Scholar].

Hooper D. C. (1999) Mode of action of fluoroquinolones. Drugs 58(Suppl. 2), 6–10. [Abstract] [Google Scholar]

Hooper D. C. (2001) Mechanisms of action of antimicrobials: Focus on fluoroquinolones. Clin. Infect. Dis. 32(Suppl. 1), S9–S15. [Abstract] [Google Scholar]

Anderson V. E.; Osheroff N. (2001) Type II topoisomerases as targets for quinolone antibacterials: Turning Dr. Jekyll into Mr. Hyde. Curr. Pharm. Des. 7, 337–353. [Abstract] [Google Scholar]

Fournier B.; Zhao X.; Lu T.; Drlica K.; Hooper D. C. (2000) Selective targeting of topoisomerase IV and DNA gyrase in Staphylococcus aureus: Different patterns of quinolone-induced inhibition of DNA synthesis. Antimicrob. Agents Chemother. 44, 2160–2165. [Europe PMC free article] [Abstract] [Google Scholar]

Price L. B.; Vogler A.; Pearson T.; Busch J. D.; Schupp J. M.; Keim P. (2003) In vitro selection and characterization of Bacillus anthracis mutants with high-level resistance to ciprofloxacin. Antimicrob. Agents Chemother. 47, 2362–2365. [Europe PMC free article] [Abstract] [Google Scholar]

Morgan-Linnell S. K.; Becnel Boyd L.; Steffen D.; Zechiedrich L. (2009) Mechanisms accounting for fluoroquinolone resistance in Escherichia coli clinical isolates. Antimicrob. Agents Chemother. 53, 235–241. [Europe PMC free article] [Abstract] [Google Scholar]

Drlica K.; Zhao X. (1997) DNA gyrase, topoisomerase IV, and the 4-quinolones. Microbiol. Mol. Biol. Rev. 61, 377–392. [Europe PMC free article] [Abstract] [Google Scholar]

Li Z.; Deguchi T.; Yasuda M.; Kawamura T.; Kanematsu E.; Nishino Y.; Ishihara S.; Kawada Y. (1998) Alteration in the GyrA subunit of DNA gyrase and the ParC subunit of DNA topoisomerase IV in quinolone-resistant clinical isolates of Staphylococcus epidermidis. Antimicrob. Agents Chemother. 42, 3293–3295. [Europe PMC free article] [Abstract] [Google Scholar]

Aldred K. J.; McPherson S. A.; Wang P.; Kerns R. J.; Graves D. E.; Turnbough C. L. Jr.; Osheroff N. (2012) Drug interactions with Bacillus anthracis topoisomerase IV: Biochemical basis for quinolone action and resistance. Biochemistry 51, 370–381. [Europe PMC free article] [Abstract] [Google Scholar]

Aldred K. J.; McPherson S. A.; Turnbough C. L. Jr.; Kerns R. J.; Osheroff N. (2013) Topoisomerase IV-quinolone interactions are mediated through a water-

metal ion bridge: Mechanistic basis of quinolone resistance. Nucleic Acids Res. 41, 4628–4639. [Europe PMC free article] [Abstract] [Google Scholar]

Pan X. S.; Gould K. A.; Fisher L. M. (2009) Probing the differential interactions of quinazolinedione PD 0305970 and quinolones with gyrase and topoisomerase IV. Antimicrob. Agents Chemother. 53, 3822–3831. [Europe PMC free article] [Abstract] [Google Scholar]

Anderson V. E.; Zaniewski R. P.; Kaczmarek F. S.; Gootz T. D.; Osheroff N. (2000) Action of quinolones against Staphylococcus aureus topoisomerase IV: Basis for DNA cleavage enhancement. Biochemistry 39, 2726–2732. [Abstract] [Google Scholar]

Pan X. S.; Yague G.; Fisher L. M. (2001) Quinolone resistance mutations in Streptococcus pneumoniae GyrA and ParC proteins: Mechanistic insights into quinolone action from enzymatic analysis, intracellular levels, and phenotypes of wild-type and mutant proteins. Antimicrob. Agents Chemother. 45, 3140–3147. [Europe PMC free article] [Abstract] [Google Scholar]

Yague G.; Morris J. E.; Pan X. S.; Gould K. A.; Fisher L. M. (2002) Cleavable-complex formation by wild-type and quinolone-resistant Streptococcus pneumoniae type II topoisomerases mediated by gemifloxacin and other fluoroquinolones. Antimicrob. Agents Chemother. 46, 413–419. [Europe PMC free article] [Abstract] [Google Scholar]

Pfeiffer E. S.; Hiasa H. (2007) Determination of the primary target of a quinolone drug and the effect of quinolone resistance-conferring mutations by measuring quinolone sensitivity based on its mode of action. Antimicrob. Agents Chemother. 51, 3410–3412. [Europe PMC free article] [Abstract] [Google Scholar]

Oppegard L. M.; Streck K. R.; Rosen J. D.; Schwanz H. A.; Drlica K.; Kerns R. J.; Hiasa H. (2010) Comparison of in vitro activities of fluoroquinolone-like 2,4- and 1,3-diones. Antimicrob. Agents Chemother. 54, 3011–3014. [Europe PMC free article] [Abstract] [Google Scholar]

Willmott C. J.; Maxwell A. (1993) A single point mutation in the DNA gyrase A protein greatly reduces binding of fluoroquinolones to the gyrase-DNA complex. Antimicrob. Agents Chemother. 37, 126–127. [Europe PMC free article] [Abstract] [Google Scholar]

Anderson V. E.; Gootz T. D.; Osheroff N. (1998) Topoisomerase IV catalysis and the mechanism of quinolone action. J. Biol. Chem. 273, 17879–17885. [Abstract] [Google Scholar]

Anderson V. E.; Zaniewski R. P.; Kaczmarek F. S.; Gootz T. D.; Osheroff N. (1999) Quinolones inhibit DNA religation mediated by Staphylococcus aureus topoisomerase IV: Changes in drug mechanism across evolutionary boundaries. J. Biol. Chem. 274, 35927–35932. [Abstract] [Google Scholar]

Barnard F. M.; Maxwell A. (2001) Interaction between DNA gyrase and quinolones: Effects of alanine mutations at GyrA subunit residues Ser(83) and Asp(87). Antimicrob. Agents Chemother. 45, 1994–2000. [Europe PMC free article] [Abstract] [Google Scholar]

Hiasa H. (2002) The Glu-84 of the ParC subunit plays critical roles in both topoisomerase IV-quinolone and topoisomerase IV-DNA interactions. Biochemistry 41, 11779–11785. [Abstract] [Google Scholar]

Hiramatsu K.; Igarashi M.; Morimoto Y.; Baba T.; Umekita M.; Akamatsu Y. (2012) Curing bacteria of antibiotic resistance: Reverse antibiotics, a novel class of antibiotics in nature. Int. J. Antimicrob. Agents 39, 478–485. [Abstract] [Google Scholar]

Martinez-Freijo P.; Fluit A. C.; Schmitz F. J.; Grek V. S.; Verhoef J.; Jones M. E. (1998) Class I integrons in Gram-negative isolates from different European hospitals and association with decreased susceptibility to multiple antibiotic compounds. J. Antimicrob. Chemother. 42, 689–696. [Abstract] [Google Scholar]

Wang M.; Tran J. H.; Jacoby G. A.; Zhang Y.; Wang F.; Hooper D. C. (2003) Plasmid-mediated quinolone resistance in clinical isolates of Escherichia coli from Shanghai, China. Antimicrob. Agents Chemother. 47, 2242–2248. [Europe PMC free article] [Abstract] [Google Scholar]

Robicsek A.; Jacoby G. A.; Hooper D. C. (2006) The worldwide emergence of plasmid-mediated quinolone resistance. Lancet Infect. Dis. 6, 629–640. [Abstract] [Google Scholar]

Poirel L.; Cattoir V.; Nordmann P. (2008) Is plasmid-mediated quinolone resistance a clinically significant problem?. Clin. Microbiol. Infect. 14, 295–297. [Abstract] [Google Scholar]

Carattoli A. (2013) Plasmids and the spread of resistance. Int. J. Med. Microbiol. 303, 298–304. [Abstract] [Google Scholar]

Tran J. H.; Jacoby G. A. (2002) Mechanism of plasmid-mediated quinolone resistance. Proc. Natl. Acad. Sci. U.S.A. 99, 5638–5642. [Europe PMC free article] [Abstract] [Google Scholar]

Xiong X.; Bromley E. H.; Oelschlaeger P.; Woolfson D. N.; Spencer J. (2011) Structural insights into quinolone antibiotic resistance mediated by pentapeptide repeat proteins: Conserved surface loops direct the activity of a Qnr protein from a Gram-negative bacterium. Nucleic Acids Res. 39, 3917–3927. [Europe PMC free article] [Abstract] [Google Scholar]

Sun H. I.; Jeong da U.; Lee J. H.; Wu X.; Park K. S.; Lee J. J.; Jeong B. C.; Lee S. H. (2010) A novel family (QnrAS) of plasmid-mediated quinolone resistance determinant. Int. J. Antimicrob. Agents 36, 578–579. [Abstract] [Google Scholar]

Lahey Clinic. qnr Numbering and Sequence (Jacoby G. A., editor. , Ed.) http://www.lahey.org/qnrstudies/ (accessed January 9, 2014).

Tran J. H.; Jacoby G. A.; Hooper D. C. (2005) Interaction of the plasmid-encoded quinolone resistance protein Qnr with Escherichia coli DNA gyrase. Antimicrob. Agents Chemother. 49, 118–125. [Europe PMC free article] [Abstract] [Google Scholar]

Tran J. H.; Jacoby G. A.; Hooper D. C. (2005) Interaction of the plasmid-encoded quinolone resistance protein QnrA with Escherichia coli topoisomerase IV. Antimicrob. Agents Chemother. 49, 3050–3052. [Europe PMC free article] [Abstract] [Google Scholar]

Robicsek A.; Strahilevitz J.; Jacoby G. A.; Macielag M.; Abbanat D.; Park C. H.; Bush K.; Hooper D. C. (2006) Fluoroquinolone-modifying enzyme: A new adaptation of a common aminoglycoside acetyltransferase. Nat. Med. 12, 83–88. [Abstract] [Google Scholar]

Guillard T.; Cambau E.; Chau F.; Massias L.; de Champs C.; Fantin B. (2013) Ciprofloxacin treatment failure in a murine model of pyelonephritis due to an AAC(6′)-Ib-cr-producing Escherichia coli strain susceptible to ciprofloxacin in vitro. Antimicrob. Agents Chemother. 57, 5830–5835. [Europe PMC free article] [Abstract] [Google Scholar]

Yamane K.; Wachino J.; Suzuki S.; Kimura K.; Shibata N.; Kato H.; Shibayama K.; Konda T.; Arakawa Y. (2007) New plasmid-mediated fluoroquinolone efflux pump, QepA, found in an Escherichia coli clinical isolate. Antimicrob. Agents Chemother. 51, 3354–3360. [Europe PMC free article] [Abstract] [Google Scholar]

Cattoir V.; Poirel L.; Nordmann P. (2008) Plasmid-mediated quinolone resistance pump QepA2 in an Escherichia coli isolate from France. Antimicrob. Agents Chemother. 52, 3801–3804. [Europe PMC free article] [Abstract] [Google Scholar]

Hansen L. H.; Sorensen S. J.; Jorgensen H. S.; Jensen L. B. (2005) The prevalence of the OqxAB multidrug efflux pump amongst olaquindox-resistant Escherichia coli in pigs. Microb. Drug Resist. 11, 378–382. [Abstract] [Google Scholar]

Kim H. B.; Wang M.; Park C. H.; Kim E. C.; Jacoby G. A.; Hooper D. C. (2009) oqxAB encoding a multidrug efflux pump in human clinical isolates of Enterobacteriaceae. Antimicrob. Agents Chemother. 53, 3582–3584. [Europe PMC free article] [Abstract] [Google Scholar]

San Millan, A., Escudero, J., Gifford, D., Mazel D., & MacLean C.R. Multicopy plasmids potentiate the evolution of antibiotic resistance in bacteria. Nat Ecol Evol 1, 0010 (2017). https://doi.org/10.1038/s41559-016-0010.

Mitscher L. A. (2005) Bacterial topoisomerase inhibitors: Quinolone and pyridone antibacterial agents. Chem. Rev. 105, 559–592. [Abstract] [Google Scholar]

Martinez-Martinez L.; Pascual A.; Garcia I.; Tran J.; Jacoby G. A. (2003) Interaction of plasmid and host quinolone resistance. J. Antimicrob. Chemother. 51, 1037–1039. [Abstract] [Google Scholar]

Jacoby G. A. (2005) Mechanisms of resistance to quinolones. Clin. Infect. Dis. 41(Suppl. 2), S120–S126. [Abstract] [Google Scholar]

Poole K. (2007) Efflux pumps as antimicrobial resistance mechanisms. Ann. Med. 39, 162–176. [Abstract] [Google Scholar]

Goldman J. D.; White D. G.; Levy S. B. (1996) Multiple antibiotic resistance (mar) locus protects Escherichia coli from rapid cell killing by fluoroquinolones. Antimicrob. Agents Chemother. 40, 1266–1269. [Europe PMC free article] [Abstract] [Google Scholar]

Singh R.; Swick M. C.; Ledesma K. R.; Yang Z.; Hu M.; Zechiedrich L.; Tam V. H. (2012) Temporal interplay between efflux pumps and target mutations in development of antibiotic resistance in Escherichia coli. Antimicrob. Agents Chemother. 56, 1680–1685. [Europe PMC free article] [Abstract] [Google Scholar]

http://eucast.org. Accession date: 14.12.2022.

World Health Organization. (2021). Antibiotic resistance. https://www.who.int/campaigns/world-antibiotic-awareness-week/waw-2019/antibiotic-resistance.

Azargun R, Sadeghi MR, Soroush Barhaghi MH, Samadi Kafil H , Yeganeh F, Ahangar Oskouee M, Ghotaslou R. The prevalence of plasmid-mediated quinolone resistance and ESBL-production in Enterobacteriaceae isolated from urinary tract infections (2018) Infection and Drug Resistance, VOL 11:https://doi.org/10.2147/IDR.S160720.

Snehashis Koley, Mandira Mukherjee, Prantiki Halder, Ambar Bose, Dushyant Lahre, Sumi Mukhopadhyay, Sudeshna Mallik.(2022) Clinico-microbiological Profile of Urinary Tract Infection with Special Reference to Uropathogenic E coli : Antibiotic susceptibility Pattern, Phylogenetic Background and Virulent Factor Distribution from West Bengal, India. Journal of the Indian Medical Association 120(10):48-53.

Dinesh Kumar, Amit Kumar Singh, Mohammad Rashid Ali and Yogesh Chander. Antimicrobial Susceptibility Profile of Extended Spectrum β-Lactamase (ESBL) Producing Escherichia coli from Various Clinical Samples. Infectious Diseases: Research and Treatment 2014:7 1–8 doi:10.4137/IDRT.S13820.

Masoud, S.M.; Abd El-Baky, R.M.; Aly, S.A.; Ibrahem, R.A. Co-Existence of Certain ESBLs, MBLs and Plasmid Mediated Quinolone Resistance Genes among MDR E. coli Isolated from Different Clinical Specimens in Egypt. Antibiotics 2021, 10, 835. https://doi.org/10.3390/ antibiotics10070835.

Biedenbach, D. J., Moet, G. J., & Jones, R. N. (2004). Occurrence and antimicrobial resistance pattern comparisons among bloodstream infection isolates from the SENTRY Antimicrobial Surveillance Program (1997–2002). Diagnostic microbiology and infectious disease, 50(1), 59-69.

Kantele, A., & Lääveri, T. (2022). Extended-spectrum beta-lactamase-producing strains among diarrhoeagenic Escherichia coli—Prospective traveller study with literature review. Journal of Travel Medicine, 29(1), taab042.

Ibrahim, D. R., Dodd, C. E., Stekel, D. J., Meshioye, R. T., Diggle, M., Lister, M., & Hobman, J. L. (2023). Multidrug-Resistant ESBL-Producing E. coli in Clinical Samples from the UK. Antibiotics, 12(1), 169.

Leila Nasehi, Fereshteh Shahcheraghi, Vajihe Sadat Nikbin,& Shoeib Nematzadeh. PER, CTX-M, TEM and SHV Beta-lactamases in Clinical Isolates of Klebsiella pneumoniae Isolated from Tehran. Iranian Journal of Basic Medical Sciences Vol. 13, No. 3, Summer 2010, 111-118 Received: Dec 7, 2009; Accepted: Feb 24, 2010 Iran J Basic Med Sci, Vol. 13, No. 3, Summer 2010 111.

Appendix

Age Vx CEZ

Chi-Square Tests

	Value	df	Asymptotic Significance (2-sided)
Pearson Chi-Square	176.827[a]	200	0.880
Likelihood Ratio	99.103	200	1.000
N of Valid Cases	287		

a. 287 cells (94.7%) have expected count less than 5. The minimum expected count is .00.

Age Vx CAZ

Chi-Square Tests

	Value	df	Asymptotic Significance (2-sided)
Pearson Chi-Square	192.407[a]	100	0.000
Likelihood Ratio	34.353	100	1.000
N of Valid Cases	287		

a. 186 cells (92.1%) have expected count less than 5. The minimum expected count is .01.

Age Vx CIP

Chi-Square Tests

	Value	df	Asymptotic Significance (2-sided)
Pearson Chi-Square	163.465[a]	200	0.972
Likelihood Ratio	167.873	200	0.952
N of Valid Cases	287		

a. 297 cells (98.0%) have expected count less than 5. The minimum expected count is .01.

Age Vx LFX

Chi-Square Tests

	Value	df	Asymptotic Significance (2-sided)
Pearson Chi-Square	157.816[a]	200	0.988
Likelihood Ratio	116.832	200	1.000
N of Valid Cases	287		

a. 287 cells (94.7%) have expected count less than 5. The minimum expected count is .01.

Gender Vx CEZ

Chi-Square Tests

	Value	df	Asymptotic Significance (2-sided)
Pearson Chi-Square	15.571[a]	6	0.016
Likelihood Ratio	12.870	6	0.045
N of Valid Cases	287		

a. 8 cells (66.7%) have expected count less than 5. The minimum expected count is .01.

Gender Vx CAZ

Chi-Square Tests

	Value	df	Asymptotic Significance (2-sided)
Pearson Chi-Square	.605[a]	3	0.895
Likelihood Ratio	0.621	3	0.892
N of Valid Cases	287		

a. 6 cells (75.0%) have expected count less than 5. The minimum expected count is .03.

Gender Vx CIP

Chi-Square Tests

	Value	df	Asymptotic Significance (2-sided)
Pearson Chi-Square	2.288[a]	6	0.891
Likelihood Ratio	3.415	6	0.755
N of Valid Cases	287		

a. 8 cells (66.7%) have expected count less than 5. The minimum expected count is .01.

Gender Vx LFX

Chi-Square Tests

	Value	df	Asymptotic Significance (2-sided)
Pearson Chi-Square	4.205[a]	6	0.649
Likelihood Ratio	4.603	6	0.596
N of Valid Cases	287		

a. 8 cells (66.7%) have expected count less than 5. The minimum expected count is .03.

Application type Vx CEZ

Chi-Square Tests

	Value	df	Asymptotic Significance (2-sided)
Pearson Chi-Square	24.253[a]	4	0.000
Likelihood Ratio	28.973	4	0.000
N of Valid Cases	287		

a. 3 cells (33.3%) have expected count less than 5. The minimum expected count is .19.

Application type Vx CAZ

Chi-Square Tests

	Value	df	Asymptotic Significance (2-sided)
Pearson Chi-Square	2.916[a]	2	0.233
Likelihood Ratio	2.485	2	0.289
N of Valid Cases	287		

a. 3 cells (50.0%) have expected count less than 5. The minimum expected count is .75.

Application type Vx CIP

Chi-Square Tests

	Value	df	Asymptotic Significance (2-sided)
Pearson Chi-Square	9.251[a]	4	0.055
Likelihood Ratio	9.841	4	0.043
N of Valid Cases	287		

a. 3 cells (33.3%) have expected count less than 5. The minimum expected count is .38.

Application type Vx LFX

Chi-Square Tests

	Value	df	Asymptotic Significance (2-sided)
Pearson Chi-Square	3.779[a]	4	0.437
Likelihood Ratio	4.728	4	0.316
N of Valid Cases	287		

a. 3 cells (33.3%) have expected count less than 5. The minimum expected count is .75.

Microorganism type Vx CEZ

Chi-Square Tests

	Value	df	Asymptotic Significance (2-sided)
Pearson Chi-Square	13.269[a]	4	0.010
Likelihood Ratio	12.971	4	0.011
N of Valid Cases	287		

a. 4 cells (44.4%) have expected count less than 5. The minimum expected count is .02.

Microorganism type Vs CAZ

Chi-Square Tests

	Value	df	Asymptotic Significance (2-sided)
Pearson Chi-Square	.238[a]	2	0.888
Likelihood Ratio	0.339	2	0.844
N of Valid Cases	287		

a. 3 cells (50.0%) have expected count less than 5. The minimum expected count is .10.

Microorganism type Vx CIP

Chi-Square Tests

	Value	df	Asymptotic Significance (2-sided)
Pearson Chi-Square	.305[a]	4	0.990
Likelihood Ratio	0.334	4	0.988
N of Valid Cases	287		

a. 5 cells (55.6%) have expected count less than 5. The minimum expected count is .05.

Microorganism type Vx LFX

Chi-Square Tests

	Value	df	Asymptotic Significance (2-sided)
Pearson Chi-Square	10.485[a]	4	0.033
Likelihood Ratio	10.904	4	0.028
N of Valid Cases	287		

a. 4 cells (44.4%) have expected count less than 5. The minimum expected count is .10.

TURNITIN

tamara tez3

ORİJİNALLİK RAPORU

%14	%	%14	%
BENZERLİK ENDEKSİ	İNTERNET KAYNAKLARI	YAYINLAR	ÖĞRENCİ ÖDEVLERİ

BİRİNCİL KAYNAKLAR

1	Katie J. Aldred, Robert J. Kerns, Neil Osheroff. "Mechanism of Quinolone Action and Resistance", Biochemistry, 2014 Yayın	%1
2	Reham Wasfi, Samira M. Hamed, Mai A. Amer, Lamiaa Ismail Fahmy. "Proteus mirabilis Biofilm: Development and Therapeutic Strategies", Frontiers in Cellular and Infection Microbiology, 2020 Yayın	%1
3	Rebekah M. Martin, Michael A. Bachman. "Colonization, Infection, and the Accessory Genome of Klebsiella pneumoniae", Frontiers in Cellular and Infection Microbiology, 2018 Yayın	%1
4	Lorenza Putignani, Ornella Massa, Anna Alisi. "Engineered Escherichia coli as new source of flavonoids and terpenoids", Food Research International, 2013 Yayın	%1