# AN OVERVIEW ABOUT SIDEROPHORES AND ANTIMICROBIAL RESISTANCE

**Maha Roushdy Abd El Wahed [1], Alshymaa A. Ahmed [1], Rehab Mohamed Ateya [1], Marwan Elgohary [2] and Fatma Atef Ibrahim[1]**

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## Abstract

**Background:**

Iron plays pivotal roles in metabolic pathways, oxygen transport, and immune function in humans, and maintaining balanced iron availability (homeostasis) is important for a healthy body. Bacteria use a number of strategies to acquire the iron essential for growth. Iron uptake by siderophores is even essential during infections caused by many pathogenic agents since the erosion of this system significantly reduces the ability of pathogens to colonize the host. Several studies have indicated that defective production and/or function of these molecules as well as iron acquisition systems in pathogens are associated with a reduction in pathogenicity of bacteria. The iron–siderophore complexes are released into the periplasm, where they may be bound by further components of the transport systems for onward translocation to the cytoplasm or be catabolized to release the iron for uptake by alternative transport mechanisms. Both Gram-positive and Gram-negative bacteria produce siderophores under the iron deficiency conditions. Pathogenic factors encompass a wide range of substances such as bacterial toxins, adhesion factors, protective capsules, and siderophores that contribute to the colonization of pathogens in the host and increase the severity of disease. The characterization of siderophore-producing activity is usually performed by a combination of several methods. At first, bacterial colonies are screened on solid agarized media to determine whether they are capable of producing siderophores. Next, the type of siderophore can be determined on Petri dishes: hydroxamate, catecholate, or carboxylate. Gram negative bacteria are among the most significant public health problems in the world due to the high resistance to antibiotics. These microorganisms are commonly implicated in both community- and nosocomial-acquired infections. They have great clinical importance in hospitals because they put patients in the ICU at high risk and lead to high morbidity and mortality.

**Keywords:** Siderophores, Antimicrobial Resistance

1 Department of clinical pathology, faculty of medicine, Zagazig University, Alsharquia, Egypt.
2 Department of Internal medicine, faculty of medicine, Zagazig University, Alsharquia, Egypt

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## INTRODUCTION

Iron plays pivotal roles in metabolic pathways, oxygen transport, and immune function in humans, and maintaining balanced iron availability (homeostasis) is important for a healthy body ***(Page, 2019)***. Iron homeostasis occurs through regulation of duodenal absorption and recycling of iron stores ***(Tansarli et al., 2013).***

Iron is an essential element that plays an important role in the cellular reactions for all microorganisms ***(khasheii et al., 2021***). This element is involved in the biological processes such as tricarboxylic acid cycle (TCA cycle), electron transfer chain, oxidative phosphorylation, nitrogen fixation, and biosynthesis of aromatic compounds ***(Fardeau et al., 2011).***

Bacteria use a number of strategies to acquire the iron essential for growth (**Wandersman and Delepelaire , 2004** ). The most important mechanisms mobilize ferric iron (Fe3+) , the dominant iron form in oxygen rich environments, but bacteria also take up aqueous ferrous iron (Fe2+) (**Lau et al., 2016)** or readily utilize ferrous iron bound in heme (**Smith AD and Wilks , 2012 ,Contreras et al., 2014)**

When bacteria uptake sufficient iron from the extracellular environment, they can have stored iron in intracellular iron-storage proteins and use it when they are in iron deficiency (***Tosha et al., 2010)***. One of the major pathways for iron uptake and bacterial survival under iron-restricted conditions is the production of low-molecular weight iron chelating molecules for iron absorption, which are called siderophores, as well as the expression of receptors with high affinity for uptake of iron or siderophore-iron complexes (***Lankford and Byers, 1973).***

Siderophores are compounds from ancient Greek words, *sidero* 'iron' and *phore* 'carriers' meaning 'iron carriers***'(Sah and Singh ,2015)***. They are low-weight high-affinity iron chelating molecules (600-1000 Da) ,they have high affinity for ferric ions (Fe3+) but low affinity for ferrous ions (Fe2+), which are produced in response to iron deficiency by

bacteria which also known as essential virulence factors of them and their production is suppressed in the presence of iron (***khasheii et al., 2021***). Siderophores are produced extracellularly and turn iron into a soluble and absorbable form ***(Messenger and Barclay, 1983)***.

**Siderophores uptake system**

Iron uptake by siderophores is even essential during infections caused by many pathogenic agents since the erosion of this system significantly reduces the ability of pathogens to colonize the host ***(Holden and Bachman, 2015)***. Several studies have indicated that defective production and/or function of these molecules as well as iron acquisition systems in pathogens are associated with a reduction in pathogenicity of bacteria (***khasheii et al., 2021***).

The iron–siderophore complexes are recognized by uptake systems in bacteria (**Chu et al., 2010)** The translocation is driven by proteins of the TonB family and the energy-transducing complex ExbB/ExbD in the cytoplasmic membrane (***Karlsson et al.,1993 ,Larsen et al.,1999,Paquelin et al., 2001,Fardeau et al.,2011,Sverzhinsky et al., 2014).***The iron–siderophore complexes are released into the periplasm, where they may be bound by further components of the transport systems for onward translocation to the cytoplasm or be catabolized to release the iron for uptake by alternative transport mechanisms ***(Page,2019).***

**Biosynthesis of Siderophores**

Siderophore biosynthesis in bacteria is performed by several enzymes: non-ribosomal peptide synthetase (NRPS), polyketide synthase (PKS), and NRPS-independent siderophore synthetase (NIS) (***Lamb, 2015).***

**Siderophore Biosynthesis by NRPS**

Siderophores synthesized by NRPS are primarily composed of amino acids, including non-proteinogenic amino acids, linked together by peptide bonds (***Miller and Gulick, 2016, Gulick, 2009)***. NRPS are large multi-domain and multi-enzyme complexes, with each subunit responsible for attaching one amino acid to a growing peptide chain, including non-proteinogenic amino acids and hydroxy acids ***(Condurso and Bruner,2012)***. The standard NRPS architecture comprises modular sequences of adenylation (A), condensation (C), peptidyl carrier protein (P) and thioesterase (T), as well as other specific functional domains including epimerization (E), oxidation (Ox), methylation (Mt) and cyclization (Cy) (***Condurso and Bruner,2012***, ***Lazos et al.,2010***)

Most bacteria have their genes encoding NRPS and aryl acid synthesis enzymes directly regulated by iron via the repressor Fur. In some cases, NRPS are partially involved in the generation of hydroxamate and carboxylate siderophores by synthesizing a peptide backbone to which iron-coordinating residues are attached (Timofeeva, Galyamova, and Sedykh 2022).

**2. Siderophore Biosynthesis by Polyketide Synthases**

Some siderophores are synthesized by polyketide synthases. The PKS module includes a ketosynthase domain, an acyltransferase domain, and a carrier domain ***(*Keatinge-Clay, 2012, Khosla et al., 2014**).

**3. Siderophore Biosynthesis by NIS Synthetase**

Some siderophores are synthesized not by NRSP or PKS (**Barry and Challis, 2009)**, but by NRPS-independent siderophore synthetases (**Oves-Costales et al., 2009)**. NIS synthetases form siderophores containing citric acid, ketoglutarate, or succinic acid. The NIS synthetase contains an acyladenylation domain that forms, for example, citrate–AMP, providing an energy-rich bond for the condensation reaction with an amino acid or polyamine.

**Iron acquisition systems in Gram-positive and Gram-negative pathogenic bacteria**

Both Gram-positive and Gram-negative bacteria produce siderophores under the iron deficiency conditions (***Chu et al., 2010***). Gram-negative bacteria have outer membrane protein receptors that detect specific Fe3+-siderophore complexes on the cell surface. Ferric-siderophore complexes are actively transported through the cell membrane, which is an energy-dependent system consisting of outer membrane siderophore protein receptors, periplasmic binding proteins, and inner membrane transport proteins (***Winkelmann, 2002***).

After ligand binding, the receptors undergo structural changes and the iron-bearing siderophore is transported to the periplasmic space, a process supported by TonB complex which consists of TonB, ExbB, and ExbD proteins and supplies energy through proton motive force (PMF). The transfer of iron-containing siderophore to the cytosol, where iron reduction occurs, is typically mediated by ATP-binding cassette (ABC) transporters within the inner membrane (***Faraldo-G´omez and Sansom, 2003; Krewulak and Vogel, 2008; Schalk and Guillon, 2013)***.

Although the TonB, ExbB, and ExbD proteins are found in many Gram-negative bacteria, they are best known in *E. coli* cells. In this bacterium, the energy transfer process requires direct contact between TonB and OM (outer membrane) receptors (***Krewulak and Vogel, 2008; Garcia-Herrero et al., 2007)***.The expression level of TonB protein increases under the iron-restricted conditions (***Wiener, 2005***).

ExbB is a 26-KDa cytoplasmic membrane protein containing three transmembrane domains and its structure is not yet fully understood. ExbD is a 17-kDa protein that has topological similarity to TonB protein and has a transmembrane domain as well as a periplasmic domain with 90 amino acids

(***Krewulak and Vogel, 2008; Garcia-Herrero et al., 2007)***.

***The importance of siderophores production in the pathogenesis of bacteria (Siderophores as a Virulence factor)***

Pathogenic factors encompass a wide range of substances such as bacterial toxins, adhesion factors, protective capsules, and siderophores that contribute to the colonization of pathogens in the host and increase the severity of disease (***Soares and Weiss, 2015)***.

Microbes have developed strategies for obtaining Fe from their host (***Cassat and Skaar, 2013)***, which involve the expression of siderophores taking Fe from proteins bound to the host Fe ***(Diaz-Ochoa et al., 2014; Contreras et al., 2014)***. Deletion of genes regulating siderophore expression or other Fe harvesting systems is often associated with reduced virulence of pathogens, including infectious bacteria such as Salmonella and Staphylococcus ***(Cassat and Skaar, 2013; Andrews-Polymenis et al., 2010)***.

In fact, strains that can produce more siderophores are highly virulent ***(Russo et al., 2011)***, and those unable to synthesize and secrete siderophore are less capable of virulence and colonization during infection ***(Codoner et al., 2006; Caza et al., 2011).***

Both Gram-positive and Gram-negative bacteria produce siderophores under iron deficiency ***(Chu et al., 2010; Khan et al., 2018).*** Bacterial siderophores can have potent cellular effects on the host by disrupting the iron homeostasis of organelles, activating transcription pathways and influencing cellular behavior. Recently, it has been shown that iron chelation directs cells toward mitophagy, namely controlled mitochondrial autophagy ***(Allen et al., 2013)***. In addition to causing mitophagy, bacterial siderophores can induce a hypoxic reaction in host cells even under normoxic conditions via stabilizing HIF-1α in the host (***Hartmann et al., 2008*****).** HIF-1α up-regulates many genes including molecules affecting the immune system such as antimicrobial peptides and inflammatory cytokines, and is a major regulator of cellular responses to hypoxic conditions as well ***(Semenza, 2011; Palazon et al., 2014)***.

Siderophores can act as a toxin and modulator of the immune system, but it is not known whether the activation of host pathways such as HIF- 1α-regulated gene expression is eventually beneficial to the host or bacterium ***(Jin et al., 2018).***

The production of siderophores can affect the anatomical site and infection pattern. In mouse models of pneumonia, the infection of wild-type mice with Ybt+strains of Klebsiella pneumoniae (yersiniabactin) caused bronchopneumonia with moderate bacterial density in the lungs and spleen ***(Bachman et al., 2012).***

***Examples of Bacteria in which Siderophores are Virulence factor***

**A-E.coli**

**Siderophore systems**

*E. coli* are equipped with siderophores that increase their virulence: enterobactin and salmochelin (catecholate siderophores), aerobactin (a mixed-type siderophore), and yersiniabactin (phenolate siderophore)(Sora et al. 2021).

Enterobactin is produced by nearly all E. coli strains and produced by many other pathogenic enterobacteria, including Salmonella spp. and Klebsiella spp. (**Crosa and Walsh, 2002 ,Ratledge and Dover, 2000**).The genes responsible for enterobactin biosynthesis and transport are grouped in a single contiguous gene cluster entEBG(AC) **(Crosa and Walsh, 2002).**Enterobactin is found in both pathogenic and non-pathogenic E. coli( **Ratledge and Dover, 2000)**but seems to play some role in ExPEC virulence. It has been demonstrated that modification of enterobactin through glycosylation by IroB results in the generation of salmochelins ***(Fischbach et al.,2006).***

Aerobactin is another siderophore commonly harbored in ExPECs. Similar to salmochelin, this siderophore is also encoded by ColV and ColBM plasmids (**Sarowska et al., 2019, Johnson et al.,2006)** and its biosynthesis is driven by enzymes encoded by the iucABCD (iron uptake chelate) genes (**Carbonetti and Williams, 1984)** .Compared to commensal strains, aerobactin biosynthetic genes are more frequently detected in pathogenic E. coli strains isolated from food-producing animals (**Dozois et al., 1992,Lafont et al., 1987,Linggood et al.,1987).**Moreover, compared to the wild-type, the virulence of an APEC strain, deficient in aerobactin synthesis and uptake, is reduced in a chicken systemic infection model (**Dozois et al.,2003).**It has also been shown that aerobactin contributes to iron uptake in vivo in a UTI model (***Garciaet al.,2011*****).** Compared to enterobactin, very low aerobactin concentrations are sufficient to stimulate bacterial growth. Moreover, enterobactin binds to albumin in serum with a consequent low amount of iron sequestered from transferrin; iron uptake by aerobactin is more efficient since it can acquire more iron from transferrin than enterobactin (**Konopka et al.,1982, Konopka and Neilands, 1984, Williams and Carbonetti, 1986).**

**B-Klebseilla pneumonia**

Siderophores supply iron for *K. pneumoniae* replication, they also induces inflammation and bacterial spread. Siderophore-dependent progression from pneumonia to bacteremia necessitates activation of the host transcriptional regulatory protein Hypoxia-inducible factor 1-alpha (HIF-1α) by iron chelation **(*Holden et al., 2016)***.

*K. pneumoniae* secrete variety of siderophores such as Enterobactin (Ent), which is encoded in the *K. pneumoniae* core genome, is one of the common

catecholates produced by *K. pneumoniae* **(*O'Brien and Gibson, 1970*)**. Because Ent is a prevalent siderophore, the innate immune system has created a way to bind it, preventing bacteria from obtaining iron **(*Smith, 2007*)**. To overcome this, bacteria have created additional siderophores to avoid the innate immune system, which are encoded in the accessory genome **(*Hantke et al., 2003)***.

*K. pneumoniae* also secrete mixed-type siderophores such as yersiniabactin (Ybt) and aerobactin (Aer). Ybt was first discovered in *Yersinia* species and the genes encoding its production, transport and regulation are found on a transposable chromosomal fragment known as high pathogenicity island (HPI) **(*Carniel, 2001*)**. Ybt is the most prevalent virulence factor associated with human *K. pneumoniae* infections worldwide **(*Bachman et al., 2011*)**. Aer has also been identified as a significant virulence factor in *K. pneumoniae* infections. Aer is typically plasmid-encoded **(*Nassif and Sansonetti, 1986)***.

**Transport of Fe–Siderophores complexes into the Cell**

There are different systems used by microorganisms to transport Fe–siderophore complexes. The transport systems differ between Gram-positive bacteria and Gram-negative bacteria. In Gram-negative bacteria, the pathway for the Fe–siderophore complex to enter the cell is arranged so that Fe chelates are transported across the outer membrane, the periplasm, and the cytoplasmic membrane by discrete transporters. The proteins required for each transport step are localized in different cell membrane compartments and have specific energy requirements ***(Ferguson and Deisenhofer, 2002)***.

**Classification of siderophores**

More than 500 siderophores have been identified since the discovery of the first three siderophores, namely mycobactin, ferrichrome and coprogen from 1949 to 1952 (***Hider and Kong, 2010).*** Bacterial siderophores are divided into three major families based on the chemical groups involved in iron binding**:** catecholates, hydroxamates, and carboxylates ***(Crumbliss and Harrington, 2009),*** and siderophores with mixed ligands that are classified into four groups of catecholate hydroxymate, phenolate hydroxymate, citrate catecholate and citrate hydroxymate. All families use negatively charged oxygen atoms to bind ferric iron, but each family has different properties that affect its affinity for iron ***(Miethke and Marahiel, 2007).***

**Catecholate type siderophores:**

This type of siderophore is only found in bacteria ***(Paul and Dubey, 2014)***. The main catecholate siderophores include enterobactin, bacillibactin, and vibriobactin ***(Hider and Kong, 2010).*** Enterobactin is a cyclic trimer of 2,3-dihydroxybenzoyl-L-serine isolated from various intestinal and pathogenic bacteria like E. coli ***(Raymond et al., 2003).*** Salmochelin is the glycosylated form of enterobactin containing two glucose-bearing catecholes in C-5 position that is isolated from uropathogenic Escherichia coli and Salmonella enterica ***(Raymond et al., 2003; Bister et al., 2004)***. The catecholate group of siderophores also forms an hexadentate octahedral complex by taking two oxygen atoms to chelate iron ***(Saha et al., 2016).*** Bacillibactin, which is isolated from Bacillus subtilis and other Bacillus species, has a tri-ester ring with an L-threonine scaffold, each threonine amine is added to the glycine bound to 2,3-dihydroxybenzoic acid ***(Dertz et al., 2006).***

**Methods for Siderophore Detection and Characterization**

The characterization of siderophore-producing activity is usually performed by a combination of several methods. At first, bacterial colonies are screened on solid agarized media to determine whether they are capable of producing siderophores. Next, the type of siderophore can be determined on Petri dishes: hydroxamate, catecholate, or carboxylate (Timofeeva et al. 2022).

For a more detailed examination, siderophores can be identified by HPLC, with NMR and mass spectrometry also used to establish the structure. Gene expression analysis is used to establish the changes in the transcriptional activity of genes depending on the Fe concentration in the medium. This method allows one to establish the genes responsible for the siderophore-producing activity(Timofeeva et al. 2022).

**1. Method for Determining the Presence of Siderophore-Producing Activity with Chromium Azurolsulfonate (CAS)**

The ability of microorganisms to produce siderophores is usually determined by the chromium azurolsulfonate (CAS) assay (**Schwyn and Neilands, 1987**). The chromazurol X Fe(III) X hexadecyltrimethylammonium bromide (HDTMA) ternary complex is an indicator: when the potent chelator removes Fe from the dye, its color changes from blue to orange (**Schwyn and Neilands, 1987**).

This method is highly sensitive and allows one to detect siderophores on the supernatant of the culture liquid(Timofeeva et al. 2022). Siderophores secreted by selected bacterial cultures can be quantitatively analyzed by growing the bacterial cultures in the Modi medium. In this case, the amount of siderophore is measured spectrophotometrically (**Schwyn and Neilands, 1987**)

Solid agar medium containing CAS is also used for the qualitative determination of siderophore

production. Orange halos around the colonies on blue agar indicate the excretion of siderophores.
Both methods require the CAS reagent to be prepared according to Schwyn and Neilands (**Schwyn and Neilands, 1987**)

**2. Identification of Catechin and Hydroxamate Groups**

The technique described above does not determine the type of siderophore. The Arnow (**Arnow, 1937)**, Csáky (**Csáky et al.,1948)**, and Shenker (**Shenker et al., 1992** ) tests are used to analyze the type of siderophore contained in the nutrient medium. The Arnow test detects the presence of catechin groups, the Csáky test is used to detect hydroxamic groups, and the Shenker test is used to detectcarboxylates.
The Arnow method is based on the reaction between the catechol and the nitrite– molybdate reagent in an acidic medium with the formation of a yellow color. In an alkaline medium, the color changes to an intense orange–red color. The color development occurs at room temperature for 5 min. If a catecholate siderophore is present, the solution stains orange– red. The intensity of the staining depends on the amount of catechol present (**Arnow,1937)**
The Csáky test detects hydroxamate-type siderophores by the formation of a stained complex (**Csáky et al., 1948)**. Dark pink staining indicates the presence of hydroxamates in the solution.

**3. HPLC, NMR, and Mass-Spectroscopy**

Fractions are lyophilized and reduced with D2O (vibrioferrin, aminohelin) or deuterated MeOH to obtain 1H-NMR and correlation spectroscopy. Siderophores are quantified by 1H-NMR with the addition of an internal sodium benzoate standard for vibrioferrin or by UV–visible emission using the literature extinction coefficients for acidified solutions of DHBA, aminohelin, nitrohelin, protochelin, and azotobactin (**Palanché et al.,2004,Cornish and Page,1998).**
Hydroxamates are isolated from liquid cultures by benzyl alcohol extraction and purified by gel filtration and HPLC. Hydroxamates have a characteristic absorption maximum at 420–423 nm. By combining cyclic voltammetry of Fe complexes with hydroxamate with mass spectra, the molecular weights of the compounds can be determined. To prove the presence of hydroxamic acids, reductive hydrolysis in 57% hydrogen iodide acid is used, resulting in the formation of ornithine, which is determined by tandem gas chromatography and mass spectrometry (**Fekete et al.,1989** ).Given the differences in the siderophore absorption profile, one can determine specific siderophores compound in complex with Fe and individually.
A recent advance in siderophore research is using electrospray and high-resolution liquid chromatography ionization mass spectrometry (HR–LC–MS) techniques that exploit the characteristic isotope structure of 54Fe–56Fe associated with organic chelates (**Baars et al., 2014** ,**Lehner et al., 2013** , **Deicke et al., 2014** ).The species thus identified can then be characterized by analyzing the tandem MS and MS/MS spectra and additional UV spectroscopy and NMR data. Siderophores in supernatant extracts are analyzed by capillary liquid chromatography followed by ESI-MS or ESI-MS/MS detection (**Essén et al., 2007)**

**Antimicrobial resistance (AMR) in Gram negative Bacteria**

Gram negative bacteria are among the most significant public health problems in the world due to the high resistance to antibiotics. These microorganisms are commonly implicated in both community- and nosocomial-acquired infections. They have great clinical importance in hospitals because they put patients in the ICU at high risk and lead to high morbidity and mortality **(Hormozi *et al*., 2018).**

The mechanism of antimicrobial resistance arises from the expression of antibiotic inactivating enzymes and non-enzymatic mechanisms. Both may result from intrinsic resistance due to mutations in chromosomal genes or acquired by transfer of mobile genetic elements carrying resistance genes:

1. Mutations in chromosomal genes resulting in an increase in the expression of intrinsic resistance mechanisms (either antibiotic-inactivating enzymes or efflux pumps), permeability alterations by loss of outer membrane porins, or target modifications.
2. Horizontal transfer of mobile genetic elements carrying resistance genes, such as plasmid-encoding β-lactamases, aminoglycosides-modifying enzymes, or non-enzymatic mechanisms such as plasmid-mediated quinolone genes for fluoroquinolone resistance in Enterobacterales **(Ruppé *et al*., 2015).**

**Beta-lactam Resistance**

Beta-lactam antimicrobial agents represent the most common treatment for bacterial infections. Resistance to β-lactams is owing to**;** inactivation of antibiotics by β-lactamases, impaired penetration of drug and presence of efflux pump **(Lakshmi *et al*., 2014).**

The persistent exposure of bacterial strains to a multitude of β-lactams induced dynamic production and mutation of β-lactamases, expanding their activity even to include the newly developed β-lactam antibiotics **(Pitout and Laupland, 2008).**

**Classification of β -lactamases**

Currently, two classification schemes for β-lactamases are in use, functional classification that was described by Bush and Jacoby so that, β-lactamases are classified into four groups and Ambler's molecular classification, which divides β-lactamases into class A, C and D enzymes as well as class B metallo-enzymes **(Bush and Jacoby, 2010)**.

**1- Functional classification**

Beta-lactamase are classified based on their ability to hydrolyze specific β -lactam classes and on the inactivation properties of the β-lactamase inhibitors (clavulanic acid, sulbactam, and tazobactam). Different functional subgroups have been added to the scheme because of identification and expansion of major β-lactamase families in which variants continue to be identified on a regular basis **(Bush and Jacoby, 2010)**.

**The classification system includes 4 groups**

- **Group 1:**

Group 1 enzymes are cephalosporinases belonging to molecular class C that are encoded on the chromosomes of many Enterobacterales and a few other organisms. They are more active on cephalosporins, but not inhibited by Clavulanic acid. They are also resistant to cefamycin (such as cefoxitin).

The subgroup 1e enzymes are group 1 variants with greater activity against ceftazidime and other oxyimino-β-lactams. They have been termed extended-spectrum AmpC β -lactamases.

- **Group 2:**

Group 2 β-lactamases, including molecular classes A and D, represent the largest group of β -lactamases.

***Sub-groups:***

- **Group 2b e (extended spectrum) β-lactamase:**

These are ESBL capable of hydrolyzing penicillin, 3rd and 4th generation cephalosporin and monobactams, but are hydrolyzed by clavulanic acid.

- **Group 2b r β-lactamase:**

These include inhibitor resistant broad-spectrum β-lactamase that have acquired resistance to clavulanic acid and sulbactam but are susceptible to inhibition by tazobactam.

- **Group 2c β-lactamase:**

These includes penicillinases that hydrolyze carbenicillin more than benzylpenicillin. These are class A enzymes. They also show activity towards oxacillin.

- **Group 2d (extended spectrum) β-lactamase:**

These are class A or D enzyme and include cloxacillinase (oxacillinase) that hydrolyze cloxacillin more than benzylpenicillin and has activity against carbenicillin.

- **Group 2e β-lactamase:**

These are class A enzymes include cephalosporinase. They hydrolyze extended-spectrum cephalosporins and inhibited by clavulanic acid or tazobactam.

- **Group 2f β-lactamase:**

These are class A enzymes include carbapenemases. These are serine -based enzymes which are inhibited by clavulanic acid.

- **Group 3:**

Group 3 are the zinc-based or metallo β-lactamases (MβL), corresponding to the molecular class B, which are the only enzymes acting by the metal ion zinc. MβL can hydrolyze penicillins, cephalosporins, and carbapenems. They are not inhibited by clavulanic acid but inhibited by Ethylenediaminetetraacetic acid (EDTA).

- **Group 4:**

Group 4 is penicillinases that are not inhibited by clavulanic acid, and they do not yet have a corresponding molecular class **(Bush and Jacoby, 2010)**.

**2- Molecular Classification (Ambler)**

The molecular classification of β-lactamases, presented by Ambler in 1980, was based on the nucleotide and amino acid sequences in these enzymes. Four classes are recognized (A-D), correlating with the functional classification. Classes A, C, and D act by a serine-based mechanism while class B (MβL) need zinc for their action **(Nordmann *et al*., 2012a)**.

- **Class A β -lactamases:**

Class A β-lactamases have a serine residue in the catalytic site, a property that they share with class C and D enzymes. Most class A enzymes are often plasmid-encoded but can also be located on the bacterial chromosome. They include 'narrow spectrum' enzymes, most notably the *bla*$_{TEM}$ and *bla*$_{SHV}$ groups. TEM (named for patient Temoneira), the first plasmid-borne β-lactamase identified in Gram negative bacteria and active against aminopenicillins and early cephalosporins. SHV (sulfhydryl variant, an enzyme with similar activity to TEM, originally identified on the chromosome of *K. pneumoniae* and subsequently mobilized onto plasmids) **(Bradford, 2001)**.

ESBL and inhibitor-resistant variants began to appear after introduction of third generation cephalosporins and β-lactamase inhibitors. Other Class A β-lactamases intrinsically have this 'extended spectrum' phenotype, e.g., the CTX-M family which is named for their ability to confer resistance to cefotaxime (CTX; -M for Munich) **(D'Andrea *et al*., 2013).** Other class A enzymes are encoded on integrons, for example, Guiana extended spectrum (GES-1) from *K. pneumoniae* **(Poirel *et al*., 2012).**

Certain class A enzymes are classed as carbapenemases. The most prominent is KPC ('*Klebsiella pneumoniae* carbapenemase'), first identified in the United States in 1996 and still associated with *K. pneumoniae* **(Chong *et al*., 2018).**

- **Class B β-lactamases:**

Class B MβL, which are dependent on zinc ions for activity rather than the active-site serine found in classes A, C and D, can confer resistance to carbapenem antibiotics, in addition to other β-lactams except aztreonam, and to β-lactamase

inhibitors. There are 10 types of metallo-carbapenemases, but most of the clinically important ones, Verona integron-encoded metallo-β-lactamase (VIM), Imipenemase (IMP), New Delhi metallo-β-lactamase (NDM) **(Cornaglia *et al*., 2011)**.

The VIM enzymes can be divided into five main types, but only blaVIM-1 and variants appear common in Enterobacterales. IMP enzymes can be divided into 14 main types. The NDM enzyme has been first reported in 2009 and 15 minor variants have now been identified, in a variety of plasmids, strain types and species **(Johnson and Woodford, 2013).**

- **Class C β-lactamases:**

AmpC β-lactamases are produced by *E coli* but are less common than ESBL production in *E coli*. This enzyme is a cephalosporinase, which inactivates cephalosporins (but not cefepime) in addition to most penicillins (including β-lactam/ β-lactamase inhibitor combinations), cephamycins, and aztreonam **(Philippon *et al*., 2002).**

Chromosomally encoded AmpC are usually identified in *P. aeruginosa* and bacteria in the Enterobacterales family such as *Enterobacter* species where their production is very low level and does not elicit any clinically relevant resistance but can be induced in the presence of β-lactam agents. Nevertheless, the acquisition of transmissible plasmids from other bacteria can lead to the overproduction of AmpC β-lactamase in some organisms lacking the gene encoding for chromosomal AmpC, for example, *K. pneumonia* **(Jacoby, 2009).**

- **Class D β-lactamases:**

Ambler class D consists of a variety of enzymes, such as oxacillinase (OXA). They are poorly inhibited by clavulanic acid. Different enzymes in this diverse class can also confer resistance to penicillins, cephalosporins, extended-spectrum cephalosporins (OXA-type ESBLs), and carbapenems (OXA-type carbapenemases) **(Evans and Amyes, 2014)**.

**Carbapenems and Carbapenemases**

**Carbapenems**

Carbapenems are a class of β-lactam antibiotics with a broad spectrum of antibacterial activity. They have a structure that renders them highly resistant to most β-lactamases **(Livermore and Woodford, 2000)**. The carbapenems that are in clinical use: imipenem, meropenem, ertapenem, doripenem, panipenem-betamipron, and biapenem **(Papp-Wallace *et al*., 2011)**.

**Mechanism of resistance against carbapenems**

Bacterial resistance against carbapenems is increasing at a significant rate and has become a common problem in the primary care medicine. There are several mechanisms of antimicrobial resistance to carbapenems, the commonest of which include changes in outer membrane proteins, over expression of drug efflux pumps and carbapenem hydrolyzing enzymes. These carbapenemases are numerous and mutate continuously in response to the heavy pressure of antibiotic use **(Kumar *et al*., 2006)**.

**Carbapenemases**

Carbapenemases are a kind of β-lactamase that can hydrolyze carbapenem antibiotics. According to the Ambler classification method, carbapenemases can be divided into classes A, B, and D. Class A and class D carbapenemases are serine β-lactamases and class B carbapenemases are MβLs **(Nordmann *et al*., 2012b).**

- **Class A serine carbapenemases**

Class A carbapenemases hydrolyze a broad spectrum of β-lactams, including penicillins, cephalosporins, and aztreonam **(Queenan and Bush, 2007).**

There are four known groups of class A carbapenemases: KPC, Serratia marcescens enzyme (SME), imipenemase/non-metallo carbapenemase-A (IMI/NMC-A) and GES. The gene coding for KPC, $bla_{KPC}$, is located on transferrable plasmids. **(Van Duin and Doi, 2017)**. SME and IMI/NMC-A enzymes are chromosomally encoded.

The SME enzyme has only been found in small sub-population of *Serratia marcescens* **(Naas *et al*., 2016)**, and IMI/NMC-A enzymes have only been identified sporadically in *Enterobacter cloacae* complex isolates. GES has been found in *P. aeruginosa* predominantly but also found in *K. pneumoniae* and *E. coli* **(Diene and Rolain, 2014).**

- **Class B carbapenemases (MβLs)**

This class of β-lactamases is characterized by the ability to hydrolyze carbapenems and by its resistance to the commercially available β-lactamase inhibitors but susceptibility to inhibition by metal ion chelators. The most common MβLs families include VIM, IMP, NDM, German imipenemase (GIM), and Seoul imipenemase (SIM) enzymes. These enzymes are incorporated as gene cassettes present within a variety of integron structures or plasmid mediated. **(Datta and Wattal, 2010).**

- **Class D serine-carbapenemases (OXA β-lactamases)**

Oxacillin-hydrolyzing β-lactamases represented one of the most prevalent plasmid-encoded β-lactamase families. They had been identified mainly in the Enterobacterales and *P. aeruginosa* and were functionally described as penicillinases capable of hydrolyzing oxacillin and cloxacillin **(Queenan and Bush, 2007)**.

The OXA-48 enzyme is the most common variant, found in most of carbapenem resistant isolates. It has high hydrolysis activity toward penicillins and low hydrolysis activity toward carbapenems ***(Logan and Weinstein, 2017)*.** It is

also not affected by β-lactamase inhibitors, which is why this enzyme has recently gained attention **(Poirel *et al*., 2012)**. Other OXA β-lactamases as OXA-23, OXA-24/40, and OXA-58, are frequently found in species of *Acinetobacter* but have a relatively weak carbapenemase activity **(Tzouvelekis *et al*., 2012**).

**Colistin Resistance**

Colistin is a cationic antimicrobial peptide discovered in 1947 from Bacillus polymyxa. It entered clinical use in 1958 but was abandoned in 1970 due to reported cases of nephrotoxicity and neurotoxicity. Reintroduction of the revived antibiotic was necessary due to the emerging increase of MDR Gram negative pathogens in combination with the deficit of newer antimicrobial regimens **(Magiorakos et al., 2012).**

Antimicrobial action of colistin is based on the initial interaction of the cationic peptide and the negatively charged lipopolysaccharide of the bacterial cell membrane, leading to destabilization of the outer membrane by displacement of calcium and magnesium, enhancing the permeability of the cell envelope causing cell death through leakage of cell contents. Two forms of colistin are commercially available: colistin sulfate for oral and topical use and colistin methane sulfonate for parenteral administration **(Giamarellou and poulakou, 2009)**.

Colistin resistance was attributed to chromosomal mutations maintained in the presence of colistin selection and excessive use of it. However, they are not transferred to other organisms. Recently, the mobilized colistin resistance gene (mcr), a plasmid-mediated colistin resistance determinant was detected worldwide. This type of resistance is not related to the use of colistin, but the plasmid can be transferred between different strains and species by conjugation and transformation **(Newton-Foot *et al*., 2017)**.

Colistin was increasingly prescribed as the last resort treatment for infections caused MDR bacteria **(Biswas *et al*., 2012)**. Its use has many constraints including toxicity, hetero-resistant isolates development, and the clinical and laboratory standards institute (CLSI) warning of the limited clinical efficacy even if intermediate in vitro susceptibility results are obtained that drives clinicians to try other treatment strategies including antimicrobial combinations or newer antimicrobial agents **(CLSI, 2021)**.

**Quinolones Resistance**

The main and most clinically relevant mechanism of resistance to quinolones is specific amino acid substitutions in the quinolones targets.In addition, other chromosomal mechanisms including under expression of porins or overexpression of efflux pumps have also been described Several transferable plasmid-mediated mechanisms can also occur, being responsible for different levels of resistance***. (Aldred et al., 2014).***

**1. Target mediated Quinolone resistance**

The main mechanism leading to high-levels of fluoroquinolone resistance is the acquisition of mutations, in one or more genes, that encode the targets of these antibiotics, the type II topoisomerases (***Redgrave et al., 2014).***

The target genes are DNA gyrase subunits *gyr*A and *gyr*B, and DNA topoisomerase IV subunits *par*C and *parE*. The region in which the mutations occur, is a small DNA sequence denominated quinolone resistance determining region (QRDR) .Mutations in this region, lead to amino acid substitutions, and consequent changes of the target protein structure. This alters the fluoroquinolone-binding affinity of the enzyme and causes resistance ***(Piddock, 1999).***
The most common mutation in Gram-negatives involves a substitution at a serine 83 within the *gyr*A ***(Redgrave et al., 2014).*** Alterations in the primary target site may be further followed by secondary mutations in lower affinity binding sites. In fact, highly resistant Gram-negative bacteria characteristically carry a combination of mutations within *gyr*A and *par*C genes ***(Everett et al., 1996).***

**.Efflux pumps**

There are different families of efflux pumps with the capacity to pump out quinolones.Three quinolones efflux pumps have been described so far, QepA1, QepA2 and OqxAB. Nonetheless, while QepA efflux pumps have been found mainly in human infections, OqxAB is almost exclusively detected in animal infections ***(Aldred et al., 2014).*** The *qep*A1 gene encodes a proton-dependent efflux pump. The substrates for this pump are hydrophilic quinolones such as ciprofloxacin and norfloxacin, nonetheless, it has reduced or no effect on more hydrophobic quinolones including nalidixic acid, levofloxacin or moxifloxacin ***(Ruiz et al., 2012).*** QepA2 is another QepA-like efflux pump which presents a spectrum of substrates similar to QepA1, and only differs from this pump in two of the 511 amino acids and in the genetic environment ***(Ruiz et al., 2012).***

**Aminoglycosides Resistance**

Resistance to aminoglycosides may be mediated by different mechanisms: modification of the 16S RNA of bacterial 30S ribosomal subunit by mutation or methylation of the aminoglycoside binding site; decrease of the intracellular concentration of the antibiotic resulting from the occurrence of modifications in the bacterial outer membrane; increase of the activity of active efflux systems; decrease of the drug transport into the cell; and by enzymatic deactivation of aminoglycosides ***(Houghton et al., 2010).***

The aminoglycosides modifying enzymes are N-acetyltransferases (AAC), which deactivate the aminoglycosides by N-acetylation in positions 3, 29, and 69; Ophosphotransferases (APH) that modify

the antibiotic in positions 39 and 20 by Ophosphorylation; and O-nucleotidyltransferases (ANT) which cause aminoglycosides deactivation at positions 49 and 20 by O-nucleotidylation ***(Shakil et al., 2008).***

**Siderophores and Antimicrobial resistance (AMR)**

Siderophores constitute a key component of pathogenicity especially of Gram negative bacterial infections, they are considered as a virulence factors which act as signals leading to increased host defense. In addition, siderophores producing bacteria acquire multidrug resistance (MDR) resulting in augmentation of infections. Patients with multiple drug resistant bacterial infections are more likely to face worse outcomes, such as increased mortality and longer hospital stays ***(Wilson et al., 2016).***

Along with the global concern about the rise of antimicrobial resistance among human pathogens, fears about the simultaneously enhancement of the pathogenic capacity of bacteria started to emerge. The possibility of acquisition of both resistance and virulence traits via horizontal gene transfer could be responsible for the appearance of strains simultaneously virulent and resistant. Furthermore, it is also possible that antimicrobial agents may select strains with more virulence factors ***(Calhau, 2014).***

This could lead to serious public health problems , Multidrug resistant and virulent strains could be responsible for severe infections and antibiotic therapy would be inefficient to treat these infections, increasing morbidity and mortality rates. Despite of the realization of some studies focusing on the relation between resistance and virulence, this interplay is still not completely elucidated ***(Calhau, 2014)***.

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