Name: Chukwuemeka Chukwunonso

Matric No.: 18/MHS07/012

Course Code: PHA 206

**Question**

List and explain four (4) mechanisms of antimicrobial resistance.

**Answer**

Antimicrobial resistance (AMR or AR) is the ability of a microbe to resist the effects of medication that once could successfully treat the microbe. Antimicrobial resistance happens when microorganisms (such as bacteria, fungi, viruses, and parasites) change when they are exposed to antimicrobial drugs (such as antibiotics, antifungals, antivirals, antimalarials, and anthelmintics). Microorganisms that develop antimicrobial resistance are sometimes referred to as “superbugs”. As a result, the medicines become ineffective and infections persist in the body, increasing the risk of spread to others.

Different mechanisms may work together to confer resistance to a single antimicrobial agent. They include:

1. **Preventing Access**

In the first strategy, the antimicrobial compounds almost always require access into the bacterial cell to reach their target site, where they can interfere with the normal function of the bacterial organism. Porin channels are the passageways by which these antibiotics would normally cross the bacterial outer membrane of Gram-negative bacteria. Some of the bacteria protect themselves by prohibiting these antimicrobial compounds from entering past their cell walls. For instance, one variety of Gram-negative bacteria reduces the uptake of certain antibiotics such as aminoglycosides and ß-lactams by modifying the cell membrane porin channel frequency, size, and selectivity. Prohibiting entry in this manner will prevent these antimicrobials from reaching their intended targets that, for aminoglycosides and ß-lactams, are the ribosomes and the penicillin-binding proteins (PBPs), respectively. This mechanism has been observed in the following:

* Pseudomonas aeruginosa against carbapenems (ß-lactam antibiotics).
* Enterobacter aerogenes and Klebsiella spp. against carbapenems.
* Vancomycin intermediate-resistant S. aureus or VISA strains with thickened cell wall trapping vancomycin.
* Many Gram-negative bacteria against aminoglycosides.
* Many Gram-negative bacteria against quinolones.

**2. Eliminating Antimicrobial Agents from the Cell by Expulsion Using Efflux Pumps**

In the second strategy, the antimicrobial agents must also be present at a sufficiently high concentration within the bacterial cell. Some bacteria possess membrane proteins that act as an export or efflux pump for certain antimicrobials, extruding the antibiotic out of the cell as fast as it can enter. This results in low intracellular concentrations that are insufficient to elicit an effect. Some efflux pumps selectively extrude specific antibiotics such as macrolides, lincosamides, streptogramins, and tetracyclines, whereas others (referred to as multiple drug resistance pumps) expel a variety of structurally diverse anti-infectives with different modes of action. This strategy has been observed in the following:

* E. coli and other Enterobacteriaceae against tetracyclines.
* Enterobacteriaceae against chloramphenicol.
* Staphylococci against macrolides and streptogramins.
* Staphylococcus aureus and Streptococcus pneumoniae against fluoroquinolones.

Efflux pumps are variants of membrane pumps possessed by all bacteria, both pathogenic and non-pathogenic, to move lipophilic or amphipathic molecules in and out of their cells. Some efflux pumps are used by antibiotic-producing bacteria to pump antibiotics out of their cells as fast as the antibiotic is made. This constitutes an immunity protective mechanism for the bacteria to prevent being killed by its own chemical weapon.

**3. Inactivation of Antimicrobial Agents via Modification or Degradation**

In the third strategy, is another means by which bacteria preserve themselves. This is done by destroying the active component of the antimicrobial agent. A classic example is the hydrolytic deactivation of the ß-lactam ring in penicillin’s and cephalosporin’s by the bacterial enzymes called ß-lactamases. The process inactivates penicilloic acid, causing it to be ineffective in binding to PBPs, thereby protecting the process of cell wall synthesis. This strategy has been observed in the following:

* Enterobacteriaceae against chloramphenicol (acetylation).
* Gram-negative and Gram-positive bacteria against aminoglycosides (phosphorylation, adenylation, and acetylation).

In Less than 10 years of the clinical introduction of penicillin’s, penicillin-resistant Staphylococcus aureus was observed in a majority of Gram-positive infections in people. The initial response by the pharmaceutical industry was to develop ß-lactam antibiotics that were unaffected by the specific ß-lactamases secreted by S. aureus. However, as a result, bacterial strains producing ß-lactamases with different properties began to emerge, as well as those with other resistance mechanisms. This cycle of resistance counteracting resistance continues even today.

**4. Modification of the Antimicrobial Target**

In the fourth strategy, some of the resistant bacteria evade antimicrobials by reprogramming or camouflaging critical target sites to avoid recognition. Therefore, despite the presence of an intact and active antimicrobial compound, no subsequent binding or inhibition will take place. This strategy has been observed in the following:

* Staphylococci against methicillin and other ß-lactams (changes or acquisition of different PBPs that do not sufficiently bind ß-lactams to inhibit cell wall synthesis).
* Enterococci against vancomycin (alteration in cell wall precursor components to decrease binding of vancomycin).
* Mycobacterium spp. against streptomycin (modification of ribosomal proteins or 16S rRNA).
* Mutations in RNA polymerase resulting in resistance to the rifamycins.
* Mutations in DNA gyrase resulting in resistance to quinolones.

Here we have some examples of bacterial resistance due to target site modification:

* Alteration in PBPs reducing affinity of ß-lactam antibiotics (Methicillin-Resistant Staphylococcus aureus, S. pneumoniae, Neisseria gonorrhoeae, Group A streptococci, Listeria monocytogenes).
* Changes in peptidoglycan layer and cell wall thickness reducing activity of vancomycin: Vancomycin-resistant S. aureus.
* Changes in vancomycin precursors reducing activity of vancomycin: Enterococcus faecium and E. faecalis.
* Alterations in DNA gyrase subunits reducing activity of fluoroquinolones: Many Gram-negative bacteria.
* Alteration in topoisomerase IV subunits reducing activity of fluoroquinolones: Many Gram-positive bacteria, particularly S. aureus and Streptococcus pneumoniae.
* Changes in RNA polymerase reducing activity of rifampicin: Mycobacterium tuberculosis.