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Mini Review

Bacterial Resistance: The Global Threat

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ABSTRACT

In the last decade we have witnessed a dramatic increase in the proportion and absolute number of bacterial pathogens resistant to multiple antibacterial agents. Multidrug-resistant bacteria are currently considered as an emergent global disease and a major public health problem. The B-Debate meeting brought together renowned experts representing the main stakeholders (i.e. policy makers, public health authorities, regulatory agencies, pharmaceutical companies and the scientific community at large) to review the global threat of antibiotic resistance and come up with a coordinated set of strategies to fight antimicrobial resistance in a multifaceted approach. We summarize the views of the B-Debate participants regarding the current situation of antimicrobial resistance in animals and the food chain, within the community and the healthcare setting as well as the role of the environment and the development of novel diagnostic and therapeutic strategies, providing expert recommendations to tackle the global threat of antimicrobial resistance.

Keywords: Antibiotic consumption; Antibiotic resistance; Antibiotic stewardship; Antibiotics as growth promoters; Drug discovery; Infection control measures; Multidrug resistant bacteria; Self-medication; Surveillance; Wastewater treatment plants

INTRODUCTION

Through years and decades the people of the world were suffering tough infections which are considered dangerous in most of times or it could be lethal in numerous times. Until Alexander Fleming (the Scottish physician) came in 1922 and discovered the first Antibiotic ever which in benzyl penicillin or Penicillin G-that miracle drug originated from a culture of Staphylococcus Aurius-that changed the concept of treatment of bacterial infections in the scientific society forever. Since that time, scientists all over the world to develop new chemicals and Antibiotics to overcome infections whether Bacterial, viral or fungal infections [1].

Antimicrobial Resistance (AMR) is considered now the most serious obstacle facing the healthcare section and threatens the communities' lives. We can say that AMR is causing more than 700000 deaths worldwide annually, which is a massive number that can be avoided easily by simple steps. Antibiotic resistance are all occurs due to the misuse of drugs, missed doses, using inaccurate concentrations of drug that could be insufficient toeradicate the microorganism, using antibiotic without consultation from a physician or healthcare specialist, using concomitant medications that may interact with the antibiotic or alter its effect and pharmaceutical characteristics, giving an antibiotic in infections where the microorganism is resistant to its effect and termination of course earlier days before full control of the infection.

So, first let us know how the antibiotics work, and then we can understand later how the microbe can attack its work or even destroy its chemical structure.

We can divide antibiotics upon there mechanism of action into:

- Agents that inhibits bacterial cell wall synthesis
- Agents that inhibits bacterial protein synthesis
- Agents that inhibits bacterial nucleic acid synthesis
- Agents that interfere with metabolic pathways in bacteria

Bacteria although its tiny structure but it can develop more and more ways of resistance that we discover everyday just to save

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their lives So, do not under estimate the power of a microorganism [2].

Factors that contributes to the incidence of Bacterial Resistance:

- Drug related factors
- Doctor related factors
- Patient related factors
- Environmental factors

So, let us explain each point of these in details,

Drug-related factors:

- The fraudulent and counterfeit Antibiotics
- The availability of some Antibiotics as OTC medications in some developing countries
- The quality of manufacturing in terms of active drug concentration within the vial or capsule
- The unavailability of different concentrations from the antimicrobial drug

Doctor-related factors:

- Overuse of Antibiotics
- Increased Empiric Antibiotic use
- Inappropriate use of Antibiotics
- Lack of knowledge and training on the appropriate use of Antibiotics

Patient-related factors:

- Self-medication without medical supervision
- Non adherence to course regimens
- Lack of education
- Prescribing from patient to another if they have similar symptoms

Environmental factors:

- Poor Sanitation
- Increased travelling
- Increased Community-acquired resistance
- Overcrowdings esp. in big cities
- The use of antimicrobials in veterinary and industrial purposes.

So, let us start by clarifying the difference between:

A Bacteriostatic

The drug that Stop the growth and replication of the microorganism inside the body giving the chance to the body defense systems to control and eradicate this infection [3].

Ex: Clindamycin

A Bactericidal

The drug that kills the microorganism inside the body to eradicate the infection [4].

EX: Vancomycin

So, If the patient is immune compromised, Better use a bactericidal rather than a bacteriostatic unless the microorganism is sensitive to a definite bacteriostatic drug. Now, let's start to navigate deep inside the bacterial resistance and know more about this world Bacterial resist. Could be due to the bacterial chromosomal genome system due to the acquisition of a new mutation in constitutional genes or due to the transfer of mobile genetic elements ex: plasmids & transposons between Bacteria [5]. Plasmids are stable, extra chromosomal, circular fragments of DNA that can include active genes capable of conferring resistance to the carrier bacteria. They are transmitted between different bacterial cells by conjugation and in some occasions, this can occur only between distinct species. Intrinsicresist is responsible for the natural lack of response of certain bacterial strains to specific antibiotics, impermeable to many antibiotics ex: the genus Pseudomonas is naturally impermeable to many antibiotics [6].

LITERATURE REVIEW

Mutations also may affect the structure of the target proteins, causing a reduction in their capacity to interact with the antibiotics due to a loss of affinity. The enzyme-mediated inactivation of drugs is another method of resistance that we face though our war against bacteria, it can be due to production of lytic enzymes or by substrate modification (acetyltransferase, phosphorylase, nucleotidase) before or after their entry into the cell. Expression may be inducible, constitutive or plasmid dependant. Beta-lactamases are enzymes that inactivate the penicillins by hydrolysis of the beta-lactam ring, which is the active moiety in their structure [7]. This resistance is a population phenomenon and is more effective as larger numbers of individual organisms present. The beta-lactamase is constitutive in gram-negative organisms and remains in the periplasmic space, increasing individual efficacy.

Changing in the permeability to the antibiotics maybe due to a reduction in the capacity to transport the molecules through the porins of the external membrane (mutations providing resistance to multiple substances) Porins can provide a path through the organism membrane to hydrophilic antibiotics (due to the lipophilic nature of membranes), such as some beta-lactams, tetracyclines and floroquinolones. Amy decrease in the ability or rate of entry of these compounds can lead to resistance [8]. There is an abundance of reports of antibiotic resistance acquired through loss or functional changes of porins in a large number of organisms such as, *E. coli, P. aeruginosa, Neisseria gonorrhoeae, Enterobacter aerogenes* and *Klebsiella pneumonia.*

Change in the permeability to the antibiotics may be due to a reduction in the capacity to transport the molecules through the porins of the external membrane (mutations providing resistance to multiple substances) to the quantity of LPS reducing the absorption of hydrophobic molecules, to changes in the membrane transport protein (mutations reducing the affinity of the transporters) which maybe a channel, electrochemical potential-driven transporter, primary active transporter or electron carrier.

One more important way of resistance in some strains of bacteria (ex: S.aureus) is the expression of pumps which is responsible for the transport of such toxic compounds as drugs,

toxins throughout the cell membrane and actively pump the drug out of the cell. Bacteria pumps out the antibiotics from their cellular interior to the external environment using these special transporter proteins called efflux pumps. Inhibiting these pumps seems to be an attractive strategy at a time when novel antibiotic supplies are dwindling. Examples of antibiotics susceptible to the efflux are Quinolones and Tetracyclines. Changes in the molecular targets are usually caused by point mutations that alter the affinity between the two molecules. Although there is no increase in the rate of mutations at particular sites, there is a very large selective pressure for clonal selection in the presence of antibiotics. The target molecules maybe on the plasma membrane, such as penicillin-binding protein (methicillin-resistant staphylococci produce an additional chromosomal PBP with a heterogeneous expression and a lower affinity for methicillin), or intracellular, such as DNA-gyrase (quinolones), metabolic enzymes such as Dihydropteroate reductase (sulfonamides), & changes in the proteins of the 30s ribosomal subunit (Aminoglycosides) or 50s subunit(macrolides) occasionally resistance is due to a change in bacterial metabolism that gives rise to an alternative pathway not sensitive to the action of the antibiotic. For Example, vancomycin-resistant enterococcus produces an enzyme that makes its cell wall insensitive to the action of the glycopeptides anymore (a pentapeptide precursor with a much lower affinity for vancomycin).

Now, as resistance became more spreader & more virulent, new definitions appeared to face the scientists lately.

Multiple Drug Resistance (MDR)

Which is the antibiotic resistance shown by a certain type of microorganism to at least one antibiotic in three or more antibiotic categories?

MDR also varies in its degree into:

Extensively-Drug Resistance (XDR)

Which is the non-susceptibility of certain bacterial species to all antibiotics except two or less antibiotic categories?

Pandrug-Resistant (PDR)

Which is the non-susceptibility of certain bacterial species to all antibiotics in all antimicrobial categories?

Antifungal resistance

Not only the bacteria capable of developing resistance, but also fungi can do so. Resistance can also develop over time when fungi are exposed to antifungal drugs as inadequate treatment course or incorrect dosage Ex: Aspergillus and Candida, some species of Candida can become resistant to all types of Antifungals available which could be very hazardous in case of invasive life threatening fungal infections.

Antiviral resistance

Antiviral resistance is a major threat facing virally infected patients especially the immunocompromised ones where prolonged drug exposure and the ongoing viral replication lead to the emergence of resistant strains, Influenza viruses are continuously changing they can change from one season to another or even within the same season. As flu virus replicates the genetic map changes constantly in a way that results in the virus become more resistant to one or more of the antiviral drugs so getting annual vaccination against flu is the best way to overcome this sort of resistance, CDC recommends that everyone 6 months of age and older get vaccinated each year. Some emerging strains of influenza virus became resistant to Amantadine and Rimantadine.

HIV is a clear example of MDR viruses, it mutates rapidly under monotherapy and Cytomegalovirus can develop resistance to ganciclivir and foscarnet under treatment.

How to prevent the emergence of Antimicrobial Resistance

AMR is more than a problem that arises because of the complications of treating infectious diseases; it is a complex, divergent global challenge that affects the environment, human as well as animal health, agriculture and the economy. Given the multitude of persons, institutions and societies AMR impacts, it presents a very urgent significant ethical issue. Following on from this point; any solution to the problem of AMR will require huge collaborative efforts as well as a fair balance of benefits and burdens among those concerned patients healthcare professionals. Now, both patients as well as the healthcare professionals have many steps to follow to implement the resistance control. Therefore, we have to admit that prevention is the best way to overcome the resistance that threatens millions of lives globally.

Let's check now the rules and duties entrusted to each section involved,

For patients:

- Hand Wash:
- When it is contaminated or visibly soiled and learn how to wash it properly, regular hand hygiene is a corner step in the prevention of spread of infection.
- Don't hesitate to contact your doctor:
- Talk to your prescriber, ask him about your medicine, and learn about dosage, interactions and possible side effects.
- Know the symptoms:
- If you suspect an infection, if your infection is not getting better, talk to your doctor
- Learn about the rational use of Antibiotics:
- Not all infections need an antibiotic, if your healthcare professional says they are unnecessary then do not ask him to give you, make sure you are getting the right antibiotic, at the right dose, for the right amount of days.
- Never share your medicine with family or friends:
- Even if they suffer the same symptoms that you experienced before, every patient has its own infection that needs a drug, dosage and duration of treatment determined only by the healthcare professional according to many factors that he evaluates in each patient in every visit.
- Prepare food safely:
- Many foods that we are consuming nowadays are contaminated with bacteria, so we need to wash, clean and

cook in healthy ways determined by the healthcare institutions.
- Take your vaccines regularly

For the healthcare professionals:

- Prescribe the antibiotics cautiously:
- Make sure to keep up to date on the recommend antibiotics practices and doses
- Take the Antibiotic stewardship pledge:
- Antibiotic Stewardship it is a systemic effort to educate and direct prescribers to follow evidence-based prescribing. In order to regulate the antibiotic overuse and so reduce the antibiotic resistance, optimizing the use of antibiotics is critical to effectively treat infections, protect patients from harms caused by unnecessary antibiotic use, and combat antibiotic resistance.

CONCLUSIONS

- Antibiotic Stewardship Programs (ASPs) can help clinicians improve clinical outcomes and minimize harms by improving antibiotic prescribing. Hospital antibiotic stewardship programs can increase infection cure rates and reduce treatment failure and hospital acquired infections.
- Take your vaccines regularly:
- Taking your vaccines regularly will ensure no transmission of any bacteria or viruses to the patients
- Wash your hands:
- Follow the hand hygiene procedures, use PPE (GLOVES), sterilization of all the instruments that are introduced to the patients while diagnosis or treatment.
- Talk with your patients always:
- About the medicine prescribed, its best way for use, at which time of the day has to be taken, its side effects and interactions, aware patients always with the risk of misuse and the consequent resistance.

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