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The Rise of Super Bugs

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ABSTRACT

Widespread overuse of antibiotic as paved the way for the development of resistance, diseases which were once upon a time easily curable has become one major concern of the world. Microorganism like bacteria can quickly adapt itself against the action of the antibiotic which makes it difficult to kill them. Multidrug resistance in gram positive and gram negative bacteria becomes very difficult to treat with conventional antibiotics. Since it is very time consuming and expensive to come up with new antibiotics, scientists are trying to come up with new methods like bacteriophage therapy, vaccinations, etc. This reduces the chance of development of resistance and minimises the use of antibiotics.

Keywords: Antibiotic resistance; Bacteriophage; Superbugs; Vaccination

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INTRODUCTION

Bacteria from clinical and nonclinical settings are becoming increasingly resistant to conventionally used antibiotics. Ten years ago the primary focus of the clinical research was the increasing resistance among the gram-positive bacteria like staphylococcus, enterococcus; however, the clinical microbiologist agrees that increase in multi-resistant gram-negative bacteria pose a greater threat as they are developing resistance more rapidly and there are fewer drugs that act on gram-negative bacteria [1].

The increase in resistance is threatening our ability to treat common infectious disease, which results in prolonged illness, disability, and death. Without effective antimicrobial agents procedures such as organ transplant, diabetes management, cancer treatment and various surgical procedures have become risky, which increases the health care cost, lengthy stay and the person requires more intensive care [2].

Over the time bacteria mutate to protect themselves from antibiotics. These mutated bacteria are known as 'super bugs'. The rise of super bugs will cause an estimated 10 million deaths by 2050 [3]. In addition to that only two new antibiotics have been developed in past 30 years.

Antibiotic Resistance

It is the ability of microorganisms to combat the effects of the antibiotics.

SPREAD OF SUPERBUGS

Food Industry

Increasing antimicrobial resistance has become a significant threat to food and security, livelihood, animal health and welfare, economics and agricultural development [4]. Increasing agricultural production has led to an increase in the use of antimicrobial agents, and the use of antimicrobial agents is expected to increase by 67% in 2030. Anti-microbial agents are necessary for treatment of plant disease [4]. Global consumption of antibiotics in agriculture ranges from 63000 tonnes/year-240000 tonnes/year.

70-80% of antibiotics given to fish is excreted into the water and therefore spread through the water system. Water contaminated by pharm waste and manure from animals treated with antibiotics contribute to the spread [5]. The soil then becomes a reservoir of antimicrobial resistant agents, and therefore fresh fruits and vegetables are contaminated with antimicrobial resistant organisms. The resistant organism can develop and spread between food-producing animals and humans by direct exposure or by the food chain.

Products Used at Home

Products like household mouthwash and disinfectants are now linked to superbugs. A household mouthwash may contain chlorhexidiene, a product that is used in wide range of antiseptic products increased resistance to antibiotic colistin. Colistin is known as an "antibiotic of last resort" used to treat Klebsiella Pneumoniae that has developed resistance to other more widely used antibiotics [6] (Figure 1).

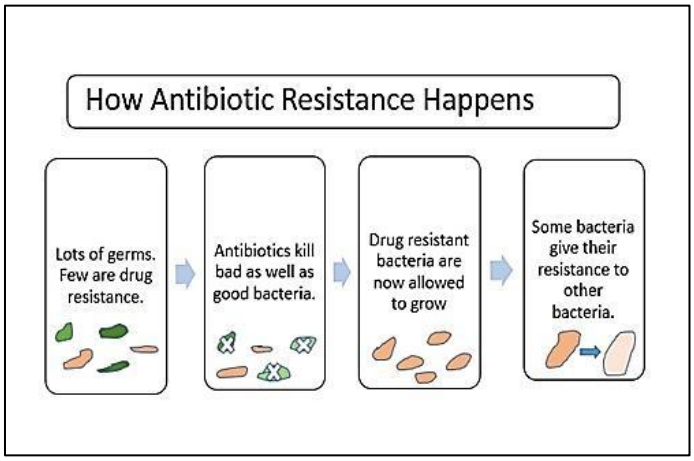

Figure 1: Development and spread of resistant microorganisms

EVOLUTION OF DRUG RESISTANCE

General Mechanism

Several mechanisms have developed in bacteria which render the antibiotic ineffective. They have many mechanisms like, chemically modifying the antibiotic, rendering it inactive by removing it from the cell or it modifies its target site which is then not recognised by the antibiotic. The most common method is enzymatic deactivation of the drug; an existing cellular enzyme is amended to react with the medicine in such a way that it no longer affects the microorganism [7,8] (Figure 2).

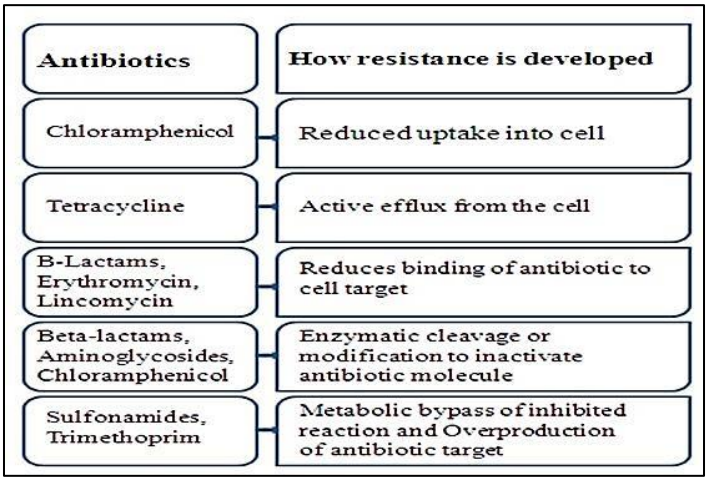

Figure 2: Antibiotic resistance

Pneumonia

Pneumonia is an inflammatory condition of the lungs primarily affecting the microscopic air sacs known as alveoli [9]. It is usually caused by bacterial infection; the air sacs may fill with fluid and pus. The infection can be life-threatening to infants, children, and adults over 65. It is a major infectious disease with significant death rate and utilisation of health resource. Community-acquired pneumonia is commonly caused by Streptococcus pneumoniea accounting for 20-60% of the case [10]. The drug-resistant Streptococcus pneumoniea has become a significant problem in managing community-acquired pneumonia. It's responsible for 1.6 million deaths annually, 1 million of which are children under 5 in developing countries [11]. Initially the use of penicillin in 1940's lead to a rapid reduction in death but due to overconsumption, resistance to penicillin developed in 1960's [11].

Mechanism and Evolution

The common mechanism of development of drug resistance in Streptococcus Pneumoniea to penicillin and beta-lactam is the modification of penicillin-binding protein (PBP), the enzyme involved in the last step of bacterial cell wall synthesis. Beta lactum binds to PBP, thereby reducing peptidoglycan synthesis and remodelling thus reducing bacterial cell wall integrity and inhibiting its growth. Development of mosaic PBP gene gave rise to resistance towards beta-lactam. The mosaic PBP gene showed a reduced affinity towards beta-lactam. The mosaic PBP gene is a continuous nucleotide sequence that differs from non-mosaic allele by up to 21% [11]; this suggests that they are non- pneumococcal in origin and it is seen in the clinically resistant strain.

Gonorrhoea

Gonorrhoea is a sexually transmitted disease caused by Nisseria Gonorrhoeae. It is one of the major health issues with high morbidity rate [12]. In 2008, WHO estimated that there are about 160 million new gonorrhoea cases among adults, there is a 21% rise since 2005. Gonorrhoea can be controlled by prevention, appropriate diagnosis and effective use of antibiotics. First, effective medicine against gonorrhoea was penicillin, which was effective for 40 years. Over last 70-80 years treatment option for gonorrhoea has diminished rapidly due to the emergence and spread of antibiotic resistance to all the drugs previously used.

Evolution, origin, and spread:

Nisseria gonorrhoea has an extraordinary ability to develop resistance towards an antimicrobial agent [13]. After the introduction of new antibiotics, it has been observed that the bacteria developed resistance towards the newly developed AMA and spread internationally in 1-2 decades after its introduction.

Most common pathways for development of resistance are:

- Drug inactivation
- Alteration in antimicrobial target
- Increased export and decreased uptake

The bug has retained resistance to recommended 1st line of defence and now is showing resistance against cephalosporin, cefixime, and ceftriaxone, drugs that are used as last remaining option for the first line of defence [14]. The most concerning mechanism in resistance development is the altering permeability of the gonococcal cell; this mechanism affects a broad range of antimicrobial agents. The resistance arises due to mutation, conjugation resistance plasmid and external gene transfer [15].

Malaria

Malaria occurs in over 90 countries worldwide. According to WHO stats 36% of the population lives in the high-risk area, 7% live in areas where malaria has never been under significant control and 29% live in areas where malaria was once transmitted at a low level or not at all, but where significant transmission has been re-established [16]. WHO stats state that each year 300-500 million malaria cases are reported making it one of the most infectious diseases. It is also responsible for 90% of 1.5 to 2 million deaths each year in African civilisation [16]. The agents of malaria are Plasmodium falciparum, vivax, ovale and malariae and it depends on the geographical region.

Drugs used:

Quinine compounds: Chloroquine - most widely used antimicrobial drug, but drastic drug resistance has reduced its use [17].

- Amodiaquine- A compound similar to chloroquine.
- Quinine along with dextroisomer quinidine- drug used as last resort.
- Other quinine-related compounds- primaquine, mefloquine.

Antifolate combination drugs: It is a combination of dihydrofolate inhibitors like trimethoprim etc. and sulpha drugs like sulphadoxine. The drugs, when used individually, has anti-malarial properties but parasitic resistance can develop, however when used in combination they have synergistic effect and helps to overcome the resistance towards individual compounds. In 2001, WHO reported development of new antifolate combination drug that is tested in Africa. It is a combination of chlorproguanil and dapsone known as lap dap. The drug is said to have better synergistic effect, greater cure rate and less likely to develop resistance because of favourable pharmacokinetic and dynamic profile [18].

Antibiotics: Tetracyclineand derivatives of doxycycline are a very potent anti-malarial drug. Areas where resistance to quinine has developed, tetracyclines are often used in combination with the quinine.

Artemisinin compounds [19]:
Current state of resistance: Resistance towards malaria is observed in 2 out of 4 species of malaria parasite that commonly infect humans. Plasmodium falciparum has developed resistance to almost all the antimicrobials; in some areas, vivax has shown resistance towards chloroquine and primaquine. Resistance can develop due to incorrect dosing, non-compliance with duration of dosing regimen, poor drug quality, drug interactions, erratic absorption and misdiagnosis

Mechanism: It has been determined that the resistance develops due spontaneous mutation which results in reduced sensitivity to a given drug. For some drugs, single point resistance is enough. The drug removes susceptible bacteria, and the resistant ones survive. A single isolate of malaria is made up of a variety of parasites which includes parasites that are highly resistant to susceptible, which therefore affects the drug action. The drug susceptibility also depends on the geographical areas [16].

Chloroquine resistance: The parasite digests the haemoglobin producing a significant amount of toxic byproduct. The parasite polymerises the byproduct in its food vacuole producing a nontoxic compound malaria pigment-haemozoin. In falciparum, the drug resistance towards chloroquine is believed to be due to increased capacity of the parasite to expel the drug at a rate that it does not allow the drug to reach its therapeutic level required for inhibition. The efflux rate is 40-50 times faster in resistant parasite and the resistance can be reversed by any drug that suppresses the efflux.

METHODS TO COMBAT RESISTANCE

When an antibiotic doesn't work, it leads to longer and more complicated illness, increased medical expenses and use of stronger antibiotics. The increase in resistance has led to increased research in finding and developing novel antibiotics. The drug requires extensive research and money, but if any antibiotic overused, resistance can eventually develop, if heavily used it can develop within two years [20]. Scientists are still looking into alternative methods to combat resistance; one such method is the use of "decoy" molecules. The decoy molecules are used along with the antibiotics. When the bacteria's resistant enzyme attacks, it will destroy the decoy molecule and not the antibiotic [21]. Clavulanic or sulbactam decoy molecules are used to prevent the resistant action of beta-lactamase enzyme from destroying penicillin drugs. Strengthening the action of existing antibiotics, the bacterial enzyme that causes resistance cannot attack the drug molecule and interfering with the bacteria’s mechanism that is responsible for resistance development instead of killing the bacteria. It can be done by interfering with the movement of bacteria’s genetic material transfer, thereby eliminating the transfer of the resistant gene. Alternate methods are used to combat the multidrug resistant bacteria.

Bacterial Interference
Also known as bacteriotherapy is a method of deliberately inoculating the host cell with nonpathogenic bacteria (commensalism), which prevents infections caused by pathogenic bacteria. For the infection to spread the bacteria needs to find a host cell. The nonpathogenic bacterium competes with the pathogen for the nutrients and adhesion to receptors. This treatment has had promising results in infections of the gut, urogenital tract, and wound sites. A bacterium that is used to generate positive health benefit is known as probiotic usage**,** and infection is avoided without triggering the host's immune system [22].

Bacteriophage Therapy

Bacteriophages are virus**es** that infect bacterial cells and were recognised in 1986 as natural killers of bacteria. Bacteriophage takes over the protein making mechanism and directs the cell to make viral protein. Bacteriophage was used for treating diseases like typhoid, dysentery, etc. till the 1920s -1940s but was stopped after World War 2 when the use of antibiotics became popular. Now that there are too many antibiotics made and increased resistance towards them, bacteriophage has once again become a field of interest [23].

Bacterial Vaccines

Bacterial vaccines have become increasingly popular, with the discovery and understanding of genome sequencing. Bacterial genomics allows scientists to scan for a particular sequence that can stimulate protective immune response against a pathogen. This process helps in quicker development of drugs and helps researchers to have a target based approach. The best target is a gene that is common in bacteria and nonhomologous to human gene which allows the bacteria to travel across the lipid membrane. Bacterial genome will help to detect conserved (Conserved sequences are similar or identical sequences which occur in DNA, and cause sequences in RNA, proteins, and carbohydrates. These sequences occur across species).sequence in bacterial species and strains worldwide. Bacterial genomics will help to produce superior vaccines [24].

Peptide-polymer

Scientists claim to have developed tiny star-shaped molecule which may effectively wipe out deadly bacteria that can no longer be killed by current antibiotics. The star shaped peptide is short chain of polymers called peptide polymers. The peptide molecule is effective in killing gram negative bacteria which develops resistance towards antibiotics quickly, and the polymers are nontoxic. When the peptides were tested on animals, it was observed that it is effective in killing the super bugs and the bugs showed no signs of resistance towards the polymer [25]. The peptide, unlike antibodies, has multiple pathways of attack which accounts for its superior performance.

Cationicpeptides

They are naturally found compounds that have hydrophilic and hydrophobic characteristics. Cationic peptides are typically found in the immune system of bacteria, plants, invertebrates and vertebrates. Even though they are not the usual synthetic drug, they do have antibacterial properties. The mechanism of cationic peptides includes interaction with the cell membrane of the bacteria leading to cell death. This method is very promising as the peptide has coevolved with commensal bacteria and yet retained its antibacterial property [25].

Cyclic D, L-a-Peptides

Unlike cationic peptide cyclic D, L-a-peptides are synthetic and amphipathic cell membrane disruptors. They are cyclic in structure and have alternate D and L amino acid. They are engineered in such a way that they attack the gram positive and gram negative cell membrane and not mammalian. These peptides can self-assemble into flat rings and form nanotubes which specifically target and puncture bacterial cell, thereby causing faster cell death.

LATEST TRENDS

Researchers Combat Antibiotic Resistance Using Smartphones

A team of UCLA researchers have developed a new method for detecting antibiotic resistance. This technology can be utilised for testing antibiotic resistance in areas which do not have labs, testing equipment and trained test diagnostician. Regular testing for antimicrobial resistance can reduce the number of death caused by bacteria and prevent the spread of resistant bacteria. Using smartphones for detection of resistance is straightforward and inexpensive and hence can help to combat the issue of complicated susceptibility testing in places with limited resources. The UCLA device has a 3-D printed platform for the smartphone, and a plate which can hold up to 96 wells and each well has a different dose of antibiotic. LED is used to illuminate the sample and with the help of the phone's camera, small changes in light transmission in each well are sensed. The image obtained is then sent to a server which automatically performs the susceptibility testing, and the result is forwarded to the Smartphone within one minute. The device has an accuracy of 98.2% [26]. It determines the lowest concentration at which the growth of the bacteria can be prevented. With this information, the physician can determine the apt concentration or combination drug that can be given to the patient. A resistant microorganism will not respond to the standard dose of that medicine [26].

Development of New Antibiotics

Teixobactin:

It is the first new antibiotic in 30 years which will help to tackle the issue of antibiotic resistance. Teixobactin is a breakthrough discovery of resistance fighting antibiotic which is obtained from the soil bacteria. This first in its class antibiotic has activity against gram positive bacteria including MSRA and all the mycobacteria. It has unique mechanism of action which is inhibiting peptidoglycan biosynthesis. It has quick bactericidal activity and inhibition of cell wall synthesis, prevents antimicrobial resistance. The testing of the drug on humans is yet to be done [27].

Pneumococcal Conjugate Vaccine (Pcv-13):

PCV-13 protects against 13 of the 90 strains of bacteria that cause the most severe infection in children and about half of the infection in adults. The vaccine does contain deactivated bacteria (not alive) therefore does not cause disease. Other than protecting those who are vaccinated, studies show that PCV-13 also lowers antimicrobial resistance by bringing down the frequency of infection and therefore reducing the use of antibiotics. It also reduces the risk of complications by opportunistic infections, and the need for broad spectrum treatment of clinical diseases like pneumonia [28]. A review on indirect effects of PCV vaccination on general population published by Lancet Global Health 2017 showed that childhood PCV programmes lead to substantial protection across the whole population within a decade. PCV vaccine can be given along with another vaccine in the immunisation schedule.

CONCLUSION

The increasing antibiotic resistance is one of the most alarming issues that need to be addressed and moderated immediately. Even though we cannot abolish the use of drugs to treat the disease, we can control the way it is used by improving the method of prescription, more selective use of the drug, improving the patient compliance so that he/she completes the antibiotics course. Resistance can also be controlled by using the combinations which are less likely to cultivate resistance or has properties that do not facilitate the development of the resistant parasite. Since most of the parasites have already developed resistance against maximum amount of drugs, the long-term solution to this problem will be the development of new affordable medicines. The new drug's effectiveness can be improved by implementing ways to use the medicine judiciously. For example, Bedaquiline is the new antibiotic for TB, the government has restricted its supply to only six centres all over India to curb the misuse of the drug. One of the most important steps towards combating antibiotic resistance is educating people about the importance of sticking to the course of the medicine and the harmful effects if the drug is misused. Taking these steps towards antibiotic resistance would reduce the pressure on researchers to come up with new antibiotics and they can channelize their focus on improving the life span of the drugs and coming up with cheaper, innovative, and antibiotic free methods to cure the disease.

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