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BULK DRUGS AND PHARMACEUTICAL INDUSTRIES

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ABSTRACT

India currently supplies about 20% of the drugs produced worldwide. About half of drugs exported from India are manufactured in Hyderabad, in the state of Telangana. Pantancheru-Bollaram is an industrial zone located approximately 32 km outside Hyderabad. In the early 1980's many bulk drug, chemical, pesticide manufacturing plants were established there. Today Pantancheru-Bollaram is home to more than 100 industries including more than 30 pharmaceutical drug manufacturers that supply nearly all leading pharmaceutical companies in the world. Until a few years ago, the effluent from PETL(write full form) was discharged into the Isakavag creek, which feeds the Nakkavagu, Manjira and eventually Godavari rivers. Following a public interest petition in 1997, the Indian Supreme Court ordered the pollution control authorities to channelize effluents from PETL through an 18km pipeline to the Amberpet mega sewage treatment plant in Hyderabad, so that the effluents could be diluted with sewage. The PETL outlet was connected to the pipeline 12 years later, in July 2009. Since then, the final treated wastewater has been discharged into the Musi river. 28 samples were taken which are subdivided into 4 tap water, 4 bore hole water and 23 environmental samples. All 23 samples contained beta-lactamase bacteria as well as carbapenems producing bacteria. It is clear that the bacteria in the waste water are developing resistance to all the antibiotics present there. The bacteria are quickly mutating and are able to attack and destroy the antibiotics, thus giving rise to super bugs which may one day be in every treated water we use. These super bugs cannot be destroyed by any antibiotics, thus the need to find a method to destroy these superbugs has to be made. The starting step is to prevent disposal of effluents from pharmaceutical industries into the sewer.

Keywords: Antibiotics, Antifungal agents, antimicrobial resistance, Multidrug resistant pathogens, Carbapenems producing Enterobacteriaceae

VALIDATION OF HYPOTHESIS:

The treatment of waste water from pharmaceutical industries is necessary to prevent the development of super bugs.

IMPORTANT FINDINGS (results, data analysis, conclusions):

Microbiological specimens were collected using ESwabs™(Copan, Brescia, Italy), a liquid-based multipurpose collection and transport system, and were transferred to the microbiology laboratory in Leipzig, Germany, within 48 h. Water samples destined for liquid chromatography–tandem mass spectrometry (LC–MS/MS) analysis were transferred to the laboratory in Nuremberg, Germany ,within 48 hrs and frozen at −80 °C. All 23 environmental samples contained ESBL as well as carbapenemase-producing bacteria (mainly Enterobacteriaceae, but also non-fermenters), of which 22 tested positive for $bla_{\text{OXA-48}}$, 10 for bla_{NDM}, 7 for bla_{KPC}, 5 for bla_{VIM}, and 5 for $bla_{\text{IMP-1}}$. Two samples, one of which derived from the Musi River, were positive for all tested carbapenemase genes. In the 10 samples from the direct vicinity of bulk drug manufacturing plants, the dominant carbapenemase gene was $bla_{\text{OXA-48}}$ (9 samples), followed by bla_{NDM} and bla_{KPC}.

INTRODUCTION:

This case study shows the effects of high concentrations of antibiotics on humans living near the pharmaceutical industries. The development of super bacteria even worsens the case. The effluent from pharmaceutical industries contains mixture of antibiotics which is not properly treated, thus creating problems for people staying in nearby villages. People there have suffered diseases. More than 56000 newborn babies die each year from infections by bacteria that are resistant to first line antibiotics. The presence of NDM-1 and carbapenemases in environmental samples has important implication for citizens reliant on public water and sanitation facilities. Microbes ability to travel within human hosts and traded animals or goods means that multidrug resistance can move around the world within a flight time of only a few hours. Visitors to a country with high prevalence of antibiotic resistance often return home colonized by MDR bacteria , which are then easily transmitted to others , including 5-10% of household members.

ACTION OF ANTIBIOTICS ON BACTERIA:

Antibiotics either destroy or slow down the growth of bacteria. Antibiotics which destroy the bacteria are known as bacteriacidal , which inhibit the bacterial growth are known as bacteriostatic. There are five methods by which bacteriostatic antibiotics affect the bacteria.

METHOD 1

Antibiotics that target the cell membrane, these antibiotics will disrupt the cell membrane function. It will alter the cell membrane structure & make it more permeable. examples of antibiotics are polymixins and polyenes (antifungal.)

METHOD 2

Inhibition of cell wall synthesis causes the bacteria to die. Example of antibiotics include Penicilin, Cephla Sporins. Humans on the other hand don't have a cell wall i.e peptidoglycan membrane therefore those antibiotics wont affect human cells.

METHOD 3

Antibiotics which inhibit the RNA & DNA synthesis in the bacteria. Drugs like Quinolenes, Nalioixic acid prevent DNA replication, while as drugs like Rifamycin inhibits RNA synthesis

METHOD 4

Drugs that inhibit protein synthesis. Protein synthesis is carried out by ribosomes which translate mRNA into proteins, bacteria need to make proteins in order to survive however there are antibiotics that target either 50s subunit or 30s subunit of the Ribosomes. Erythromycin and Chloramphenicol target the 50s subunit whereas Tetracycline, Streptomycin and Gentamycin target the 30s subunit, either way this will disrupt the ribosomes from making proteins .

METHOD 5

Inhibition of Folic acid metabolism. PABA (Para amino benzoic acid) is a precursor to Folate. Folate is essential for the synthesis of Nucleic acids, i.e Adenine and Thymine two of the four Nucleic acids that make up the DNA. Drugs like Sulfonamides and trimetoprim prevent the conversion of PABA to Folate. These drugs don't have any affect to human cells because we don't synthesize foilc acid in our cells.

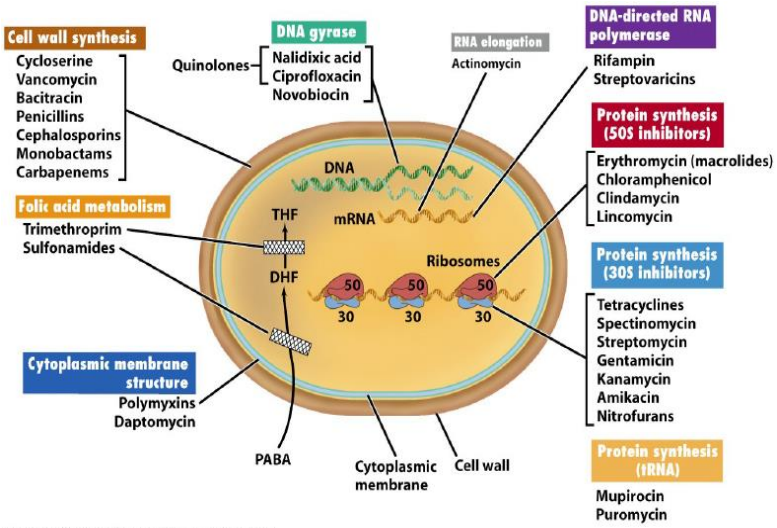

Figure 20-14 Brock Biology of Microorganisms 11/e
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ANTIBIOTIC RESISTANCE:

In the bacterial cell we have the DNA, but this is not the only genetic material, bacteria also has plasmids which are circular in shape and are smaller than DNA, they carry the resistant genes. These genes allow the bacteria to make things so that the bacteria becomes resistant to antibiotics, for the plasmids to make these resistance things, it usually has to incorporate itself to the main DNA but here the plasmid synthesizes RNA directly, in particular mRNA, this mRNA will be read by the ribosomes to make proteins and these proteins will become structures or enzymes which help the bacteria to become resistant.

There are 3 methods the bacteria resists the antibiotic:

METHOD 1

The resistant gene in the plasmid help it to make mRNA which when read by ribosomes makes proteins which turn into antibiotic degrading enzymes. One example of these type of bacteria is the betalactamases, which essentially breakdown the beta-lactam ring in the antibiotics thus making it ineffective.

METHOD 2

Efflux pump:

Sometimes the proteins become structures known as the efflux pump. Antibiotics such as Tetracycline which targets protein synthesis, the bacteria uses efflux pump to pump out the antibiotic and thus the he antibiotic is ineffective.

METHOD 3

Modifying the Antibiotic binding target:

Penicillin for example binds to penicillin binding proteins which are found in the peptidoglycan layer, however if the bacteria has the genes to modify the penicillin binding protein i.e changing the structure of the protein, the penicillin is unable to bind to the protein.

There are two ways the bacteria acquires resistance:

1. Vertical gene transfer

2. Horizontal gene transfer

In the vertical gene transfer the resistance is passed through bacterial replication. the resistant gene gets created by spontaneous mutation in the DNA during replication.

Horizontal gene transfer:

Resistance gene is transferred through 3 ways:

1. Conjugation
2. Transduction
3. Transformation

CONJUGATION:

In this method a bacteria having a resistive gene in its plasmid will attach itself to a normal bacteria. The contact point is called a PILUS. The transfer of resistive gene done by the replication of the plasmid in the normal bacteria.

TRANSDUCTION:

Virus which only attack bacteria are known as bacteria phages. The virus will inject its DNA into the bacteria, the phage DNA can then incorporate into the bacterial DNA & then after some time has passed & when the time is right the phage DNA will leave the bacterial DNA and will then begin replicating & thus destroying the bacterial DNA in the process.

While the phage DNA is being replicated, new bacteria phages are being formed within the bacteria, the virus will pack up the DNA, the viral replication will cause the bacteria to lyse, releasing the virus , however there can be a virus which carries a resistant gene accidently, therefore when this virus attacks another bacteria the resistance gene is transferred.

TRANSFORMATION

It happens when a resistive bacteria dies or lysis, the resistant genes are released and these genes can be picked up by another bacteria.

ATTEMPTED SOLUTION:

Scientists discover that Superbugs can be killed by modifying existing drugs.

Antibiotics have ‘keys’ that fit ‘locks’ on bacterial cell surfaces, allowing them to latch on. When a bacterium becomes resistant to a drug, it effectively changes the locks so the key won’t fit any more. Incredibly, scientists have found that certain antibiotics can still ‘force’ the lock, allowing them to bind to and kill resistant bacteria because they are able to push hard enough. In fact, some of them were so strong they tore the door off its hinges, killing the bacteria instantly. The study tested a powerful antibiotic called vancomycin, used as a last-resort treatment for infections like MRSA, and another called oritavancin, used to treat skin infections. We found that oritavancin pressed into resistant bacteria with a force 11,000 times stronger than vancomycin. Even though it has the same ‘key’ as vancomycin, oritavancin was still highly effective at killing resistant bacteria. Until now it wasn’t clear how oritavancin killed bacteria, but study suggests that the forces it generates can actually tear holes in the bacteria and rip them apart.

Also, it is found that the polymers to be really good at wiping out bacterial infections. They are actually effective in treating mice infected by antibiotic-resistant bacteria. At the same time, they are quite non-toxic to the healthy cells in the body. The SNAPPs are too large (about 10 nanometers) to enter healthy cells, but they create havoc in bacteria. The 16- or 32-point stars attach themselves to the superbugs and can physically

rip apart the cell wall. But the polymer can also allow ions to penetrate the cytoplasm membrane, wrecking the metabolism of the bacteria and even causing apoptosis, a type of programmed cellular death.

While, these are the solutions to kill the already existing superbugs one has to treat the viruses in the STP plant itself to eradicate the formation of superbugs.

RESULTS:

FINDINGS:

Carbapenemase-producing Enterobacteriaceae (CPE) and non-fermenters in more than 95% of our samples from Hyderabad, and the proportion of ESBL-producing organisms was 100%. Excessively high concentrations of clinically relevant antibiotics and antifungal agents were also measured in the environment. The most notable finding is the detection of fluconazole at a concentration of 236,950 µg/L (more than 20 times greater than therapeutically desired levels in the blood) in a sewage sample (s6*) from the Patancheru–Bollaram industrial zone. To our knowledge, this is the highest concentration of any drug ever measured in the environment. The uniqueness of this finding may be the result of low water flow, evaporation of water (ambient temperature was 27 °C, leading to more concentrated samples), and discharge of a production lot that may have not met quality criteria.

CONCLUSION:

Environmental pollution and insufficient wastewater management in one of the world's largest centers for bulk drug production lead to unprecedented antimicrobial drug contamination of surface, ground, and drinking water, which seems to be associated with the selection and spread of carbapenem-resistant Enterobacteriaceae and non-fermenters, such as *Acinetobacter baumannii*. The presence of ESBL and carbapenemase-producing pathogens in environmental samples from the Hyderabad metropolitan area has important implications for people in the city and surrounding countryside who are reliant on public water and sanitation facilities.

This case study has proven the immediate requirement of EIA studies on pharmaceutical industries that are causing serious health problems by polluting the water.

As there are no methods that could kill the viruses in waste water in the STP plant , the improvements that must have taken is the implementation of the process in the sewage treatment plant that could kill the viruses present in the effluents of pharmaceutical industries before it is disposed off to streams or rivers.

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