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Review Article

Drug Resistance In Various Disorders

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ABSTRACT

Drug resistance is the ability of microorganisms, such as bacteria, viruses, or parasites, to withstand the effects of drugs that were intended to kill or inhibit their growth. In developed countries, drug resistance is the primary cause of death, the burden of infectious diseases is comparatively greater, and patients with a resistance are less likely to be able to afford secondary line treatments, which typically have more complex regimens than first line drugs. Nowadays, antibiotic resistance is increasing. Some of the common drug resistances like Bacteria, Cancer, Diabetes, Leprosy, and HIV. These are the main cause of efflux protein resistance, which happens when diseases become tolerant to the pharmaceutical treatments.

DRUG RESISTANCE

Drug resistance makes antimicrobial medications, including antibiotics, ineffective and makes treating infections challenging or impossible. This raises the risk of infection spread, serious illness, disability, and death. AMR is a natural process brought about by pathogen genetic alterations over time. Antibiotics are among the many substrates that efflux proteins aggressively pump out of cells and into the surrounding environment. They are present in eukaryotic cells as well as Gram-positive and Gram- negative bacteria. Efflux proteins can be categorized into seven classes according to their energy source, general structure, and homology in protein sequence. Transmembrane proteins called multidrug efflux pumps are made by bacteria to increase their ability to survive in hostile conditions and to build resistance to antibiotics.

INTRODUCTION

BACTERIA:

Bacteria are common, largely free-living creatures that often only have one biological cell. They make up a substantial portion of prokaryotic microbes. Bacteria, which are usually a few micrometers in length, are found in most of Earth's ecosystems and were among the first living forms to emerge. Soil, water, acidic hot springs,

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radioactive waste, and the deep biosphere of the Earth's crust are all home to bacteria. Between 1013 and 1014 bacteria are present in large quantities in both humans and the majority of other animals [1].

CAUSES:

Bacteria undergo a stepwise transition from low-level to high-level resistance by consecutive changes in chromosomes [2]. In the absence of plasmids and transposons, which typically mediate high-level resistance. The first emergence of tetracycline and penicillin resistance in N. gonorrhoeae was caused by this pathway. Later, transposons containing genes highly resistant to these medications were acquired by the organism. Because of changes in the target enzymes (topoisomerases) and increased expression of membrane proteins that pump the drugs out of the cell [3].

MECHANISM OF ACTION AND DRUGS USED IN BACTERIA RESISTANCE:

MECHANISM OF ACTION	DRUGS
Inhibition of Cell wall synthesis	Penicillin's, cephalosporins, monobactams
Inhibition of Protein synthesis	Tetracyclines, aminoglycosides, macrolides
Inhibition of DNA synthesis	Fluoroquinolones
Competitive Inhibition of folic acid synthesis	Sulfonamides,Trimethoprime
Inhibition of RNA synthesis	Rifampin
Inhibit Nucleic acid synthesis	Quinolones
Bind to 50s Ribosomal subunit	Chlorophenicol, lincosamides, macrolides

DRUG RESISTANCE IN ANTIBIOTICS:

The antibiotic resistance develops when a medication can no longer effectively limit bacterial growth. When therapeutic concentrations of the antibiotics are present, bacteria develop a resistance and keep growing [4]. Antibiotics are typically effective against them, but when the microorganisms develop resistance or sensitivity, a larger concentration of the same medication is needed to provide a desired result. All bacteria have the innate ability to have some degree of low-level resistance to antibiotics, which can lead to antibiotic resistance through natural selection[5]. Sulphonamides were first introduced; the emergence of certain resistance mechanisms has prompted the use of these drugs therapeutically. But sulphonamide resistance has been documented, exposing the same resistance mechanism that persists over eight decades later [6]. The first semisynthetic penicillinase-resistant antibiotic to target strains of penicillinase-producing Staphylococcus aureus was methicillin, which was initially introduced. But not long after it started, methicillin resistance was documented. Furthermore, fluoroquinolone resistance later revealed that these medications were also used to treat Gram-positive infections, despite the fact that these treatments were first released in the 1980s to treat Gram-negative bacterial disorders [7].

CANCER:

The phrases "tumor" and "cancer" refer to pathological conditions marked by aberrant cells that have the potential to invade tissues and organs and proliferate
out of control[8].

CAUSES:

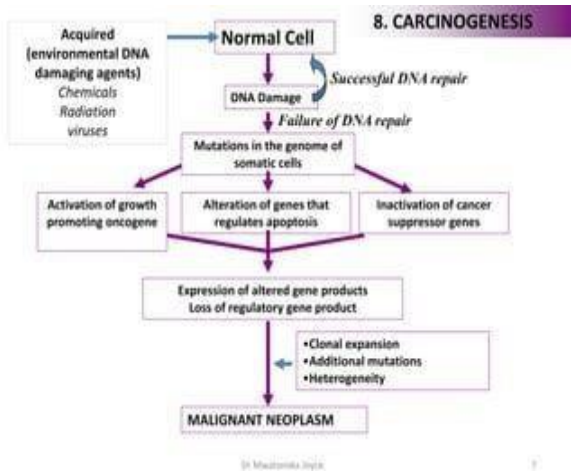
Numerous factors can contribute to cancer in various body parts. Tobacco use accounts for 22% of deaths, while poor diet, obesity, inactivity, and excessive alcohol consumption account for 10% of deaths. Other factors include infection, ionizing radiation exposure, and environmental pollutants[9]. Hepatitis B, hepatitis C, human papillomavirus infection, helicobacter pylori, immunodeficiency virus (HIV), and Epstein-Barr virus are among the illnesses that cause about 15% of cancer cases worldwide. The genes have changed, at least in part, because of these influences. Five to ten percent of cancer cases are

also caused by inherited genetic abnormalities from the patient's parents[10].

DRUGS USED IN CANCER RESISTANCE:

DNA interacting drugs:	Procarbazine, Cisplatin, Doxorubicin, Etoposide
Antimetabolites:	Mercaptopurine, fluorouracil, Methotrexate
Anti tubulin drugs:	docetaxel, Vincristine
Tyrosine kinase inhibitors:	Imatinib, Trastuzumab
Angiogenesis:	Bevacizumab

MECHANISM OF ACTION:



DRUG RESISTANCE IN CANCER:

Cancer drug resistance can arise due to various factors, including genetic mutations, tumor heterogeneity, drug metabolism changes, and activation of alternative signaling pathways within cancer cells. Additionally, the tumor microenvironment, where cancer cells interact with surrounding tissues, can contribute to resistance by providing protective conditions for cancer cell survival and growth despite treatment. Cancer therapy can be defined as a three-component system that consists of a therapy (i) that targets a population of cancer cells (ii) inside a certain host environment (iii). The range of clinical reactions is caused by the pharmacological characteristics of the treatment, as well as intrinsic and acquired physical and molecular characteristics of cancer cells and extrinsic environmental factors. The binary distinctions between intrinsic and acquired resistance have been the subject of many accounts of drug resistance in cancer; however, in reality, many tumors are or become resistant due to overlapping combinations of these mechanisms.

DIABETES:

Diabetes is a long-term metabolic disease marked by elevated blood glucose levels. Diabetes is a chronic illness that needs to be properly monitored and treated with dietary adjustments and routine habit changes.

CAUSES:

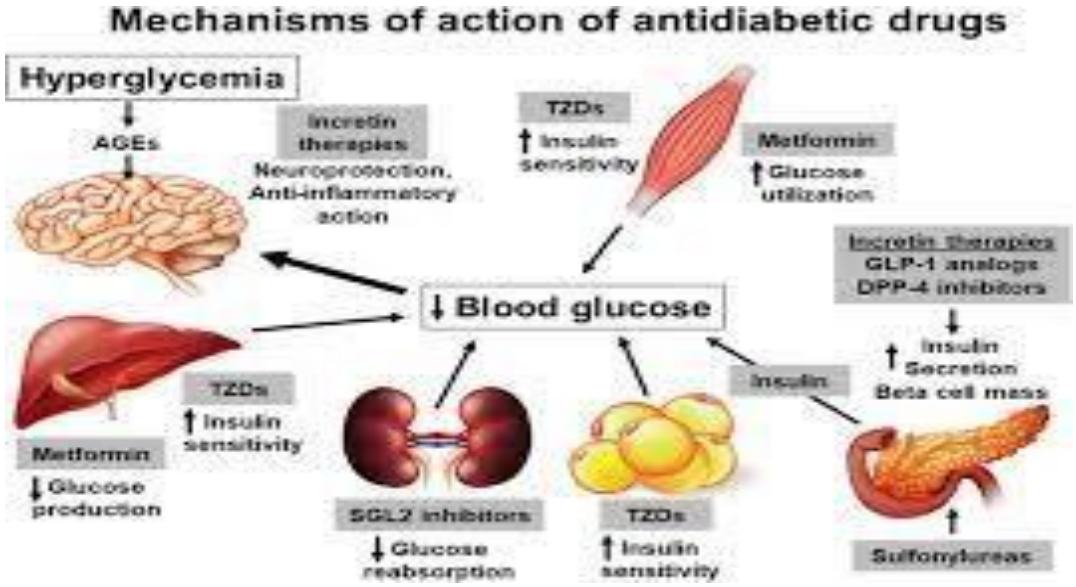
The failure of the body to either create or react to the pancreatic hormone insulin results in diabetes. Controlling blood glucose levels is one of insulin's key physiological functions. Cells require the proper amount of glucose, neither too little nor too much, as it is a crucial ingredient for cellular metabolism. Diabetes is caused by insufficient insulin secretion by the pancreas or by a lack of tissue sensitivity to the hormone; hyperglycemia, or increased blood glucose, is the main symptom of the condition. Type I or type II diabetes can be identified in the majority of people. Type II diabetes is defined by tissue resistance to the insulin that the pancreas produces, while type I diabetes is characterized by a lack of insulin production[11].

DRUGS USED IN DIABETES RESISTANCE:

Currently, six classes of oral antidiabetic drugs (OADs) are available:

- Biguanides (e.g., metformin)
- Sulfonylureas (e.g., glimepiride)
- Meglitinides (e.g., repaglinide)
- Thiazolidinediones (e.g., pioglitazone)
- Dipeptidyl peptidase IV inhibitors (e.g., sitagliptin)
- α-glucosidase inhibitors (e.g., acarbose)

MECHANISM OF ACTION:



DRUG RESISTANCE IN DIABETES:

The pancreatic islets of Langerhans beta cells secrete the peptide hormone insulin, which controls and facilitates the metabolism of protein, fats, and carbs. Insulin regulates blood glucose levels by encouraging muscle and liver cells to absorb glucose into their cells. Insulin's mutagenic properties also help to stimulate cell growth and division. Diabetes-related insulin resistance can be explained as a state in which body cells exhibit a reduced biological response to released insulin. But the main factor raising the risk of prediabetes, Type-2 diabetes, and gestational diabetes is resistance to insulin.

LEPROSY:

A chronic infectious condition called leprosy is brought on by Mycobacterium leprae or Mycobacterium lepromatosis[13]. If neglected, the condition mostly affects the skin, mucous membranes, and peripheral nerves; nerve damage and deformities may result. Utilizing dapsone, commonly known as diamino diphenyl sulphone (DDS), as a leprosy treatment[14].

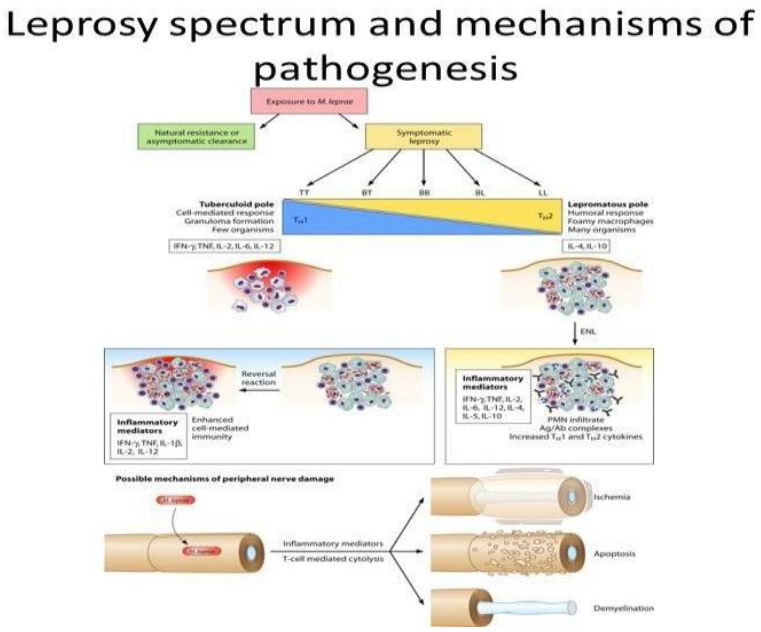
CAUSES:

According to lab testing, M. leprae grows best at temperatures between 27 and 33 C. This supports the original assumption of M. leprae's propensity to spread more quickly at colder body temperatures. This covers the skin, the membranes in the upper respiratory tract, and the nerves near the skin's surface [15]. Additionally, this strain thrives in the nine-banded armadillos, which have a natural It is primarily found in south-central United States and has a temperature of 34 C. In addition to armadillos, M. leprae has also been found in chimpanzees, mangabey monkeys, and cynomolgus macaques [16]. The genomes of M. leprae and M. lepromatosis have been identified, and they demonstrate that both strains' genetic composition includes a significant amount of pseudogenes. A number of genes necessary for the production of important enzymes for metabolic pathways are also absent. The overabundance of pseudogenes has facilitated the robust development of mycobacteria under the classification as an obligatory intracellular organism[17].

DRUGS USED IN LEPROSY RESISTANCE:

Sulfones:	e.g.: Dapsone
Phenazine Derivatives:	e.g.: Clofazime
Anti tubercular Drugs:	e.g.: Rifampacin
Others-Fluoroquinolones:	eg:Ofloxacin, Moxifloxacin
Macrolides:	e.g.: Clarithromycin
Tetracyclines:	e.g.: Minocycline

MECHANISM OF ACTION:



DRUG RESISTANCE IN LEPROSY:

The WHO suggests clofazimine plus two of the aforementioned medications plus clofazimine every day for six months, then clofazimine plus one of the medications for an additional eighteen months7. The primary cause of resistance to these medications is mutations in the target genes (Folp1, RpoB, and GyrA).

HIV:

The human immunodeficiency virus, or HIV, is a virus that attacks the body's immune system. Acquired immunodeficiency syndrome, or AIDS, is the most advanced stage of the
illness. HIV damages the body's white blood cells, reducing immunity.

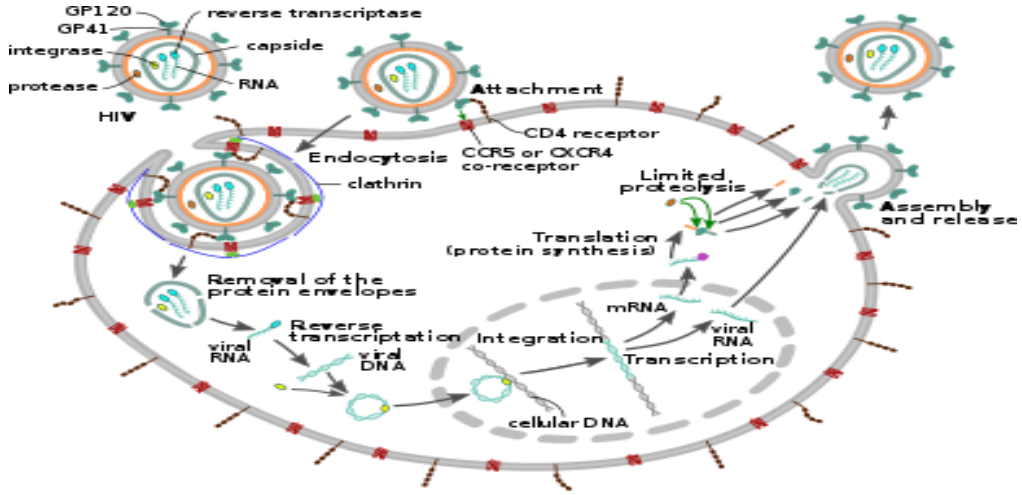
CAUSES:

Pregnancy, childbirth, and breastfeeding are the main times when HIV is passed from mother to child. It can also be spread by blood transfusions, contaminated hypodermic needles, and unprotected intercourse, including anal and vaginal sex [18]. Physiological fluids that do not transfer the virus include tears, sweat, and saliva. The risk of virus transmission during oral intercourse is negligible

DRUGS USED IN HIV RESISTANCE:

Nucleoside reverse transcriptase inhibitors:	e.g.: Zidovudine, Stavudine, Didanosine, Tenofovir
Non-Nucleoside reverse transcriptase inhibitors:	e.g: Nevirapine, Delaviridine, Efavirenz
Protease inhibitors:	e.g Amprenavir, Atazavir, Indinavir, Lopinavir, Ritonavir
Fusion inhibitors:	e.g: Marviroc
CCR5 Antagonists:	e.g : Vicriviroc ,Aplaviroc
Integrase strand transfer inhibitors	eg : Dolutegravir, Elvitegravir

MECHANISM OF ACTION:



DRUG RESISTANCE IN HIV:

Drug resistance in HIV occurs when the virus mutates and becomes resistant to the effects of antiretroviral drugs. This can happen if the virus replicates in the presence of the drug and mutations occur that allow it to evade the drug's effects. Regular monitoring and adherence to treatment regimens are essential to minimize the development of drug resistance.

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