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COURSE TITLE: PHARMACEUTICAL MICROBIOLOGY

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ASSIGNMENT: LIST AND EXPLAIN 4 MACHANISM OF ANTIMICROBIAL RESISTANCE NOTE.

FOUR MECHANISM OF ANTIMICROBIAL RESISTANCE

- Limiting uptake of a drug
- Modification of drug target
- Inactivating a drug
- Active drug efflux

Limiting uptake of a drug: there is a natural difference in the ability of bacteria to limit the uptake of antimicrobial agents. The structure and functions of the LPS layer in gram negative bacteria provides a barrier to certain types of molecules. This gives those innate resistance to certain groups of large antimicrobial agents. The mycobacteria have an outer membrane that has a high lipid content and so hydrophobic drugs such as rifampicin and the fluoroquinolones have an easier access to the cell but hydrophilic drugs have limited access. Bacterial that lack a cell wall such as mycoplasma and related species are therefore intrinsically resistant to all drugs that target the cell wall including B-lactams and glycoproteins. Gram positive bacteria do not possess an outer membrane and restricting drug access is not as prevalent. In the enterococci, the fact that polar molecules have difficulty penetrating the cell wall gives intrinsic resistance to aminoglycosides. Another gram positive bacteria, staphylococcus aureus recently has developed resistsnce to vancomycin. Of the two mechanism that S. aureus uses against vancomycin a yet unexplained mechanism allows the bacteria to produce a thickened cell wall which makes it difficult for the drug to enter the

cell and provides an intermediate resistance to vancomycin.

Modification of drug target: these are multiple components in the bacterial cell that may be targets of antimicrobial agents; and there are just as many targets that may be modified by bacteria to enable resistance of drugs. One mechanism of resistance to the B -lactam drugs used almost exclusively by gram positive bacteria is via alteration in the structure and/or number of PBPs(penicillin-binding proteins). PBPs are transpeptidases involved in the construction of peptidoglycan in the cell wall. A change in the number of PBPs impact the amount of drugs that can bind to that target. A change in structure may decrease the ability of the drug to bind or totally inhibit drug binding. Mutation in gene change causes the charge of the cell membrane surface to be positive, inhibits the binding of calcium . The resistance of drugs that target the ribosomal subunits may occur via ribosomal mutation most commonly erm genes or ribosomal protection. These mechanisms interfere with the ability of the drug to bind to the ribosome. The level of drug interference varies greatly among these mechanism. For drugs that target nucleic acid synthesis resistance is via modifications in DNA gyrase or topoisomerase IV. These mutation causes changes in structure of gyrase and topoisomerase which decrease or eliminate the ability of the drugs to bind to these components.

Drug inactivation: there are two main ways in which bacteria inactivates drugs by actual degradation of the drugs or by transfer of a chemical group to the drug. The B-lactamases are a very large group of drug hydrolyzing enzymes. Another drug that can be inactivated by hydrolyzation is tetracycline via the text gene. Drug inactivation by transfer of a chemical group to the drugs most commonly uses transfer of acetyl, phosphoryl, and adenyl groups. There are a large number of transferases that have been identified. Acetylation is the most diversely used mechanism and is known to be used against the aminoglycosides, chloramphenicol, the streptogramins and the fluoroquinolones are known to be used primarily against the aminoglycosides.

Active drug efflux: bacteria possess chromosomally encoded genes for efflux pumps. Some are expressed constitutively and other are induced or over-expressed under certain environment stimuli or when a suitable substrate is present. The efflux pumps function primarily to rid the bacterial cell of toxic substance and many of these pumps will transport a large variety of compounds. The resistance capability of many of these pumps is influenced by what carbon source is available. Most bacteria possess many different types of efflux pumps.