Version 2

Antibiotics

-Important -Extra -Notes

-In boy's slides -In girl's slides

In this link, you will find any correction or notes unmentioned in the team's work. Please check the link below Frequently.
https://docs.google.com/document/d/1WvdeC1atp7J-ZKWOUSukSLsEcosjZ0AqV4z2VcH2TA0/edit?usp=sharing

MICROBIOLOGY TEAM 438

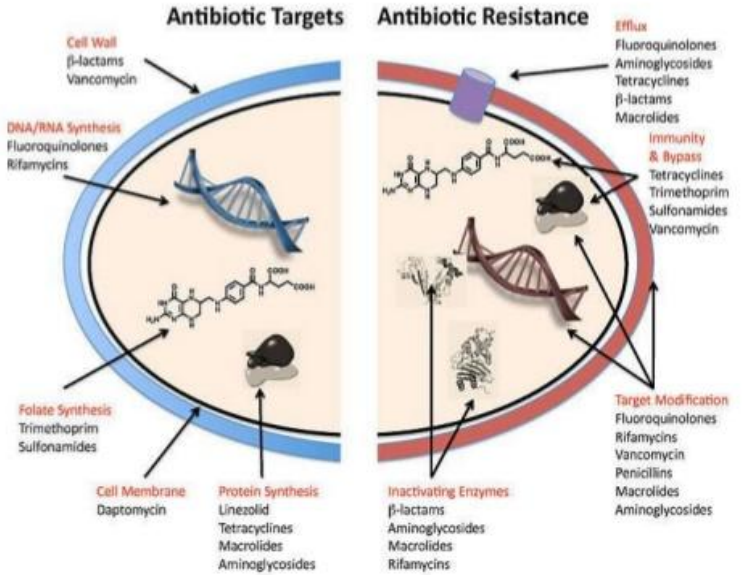
Objectives:

★ **By the end of this lecture the student should be able to:**

- Define antibiotics, chemotherapy and selective toxicity
- Describe the difference between bactericidal and bacteriostatic antibiotics
- Recognize the narrow and broad spectrum antibiotics
- Define the therapeutic index
- Recall the mechanism of action of antimicrobial agents.
- Recognize the various classes of antimicrobial agents

  (action, spectrum and side effects)

- Explain the criteria for an ideal antimicrobial



Antimicrobial Agents

Antibiotics:

Natural compounds produced by microorganism which inhibit the growth of other microorganism (survival mechanism).

Chemotherapy:

Unnatural compounds that are produced synthetically (in laboratories).

Antimicrobial Agent Activity:

- Bactericidal: kills the bacteria.
- Bacteriostatic: prevents multiplication of the bacteria.

Spectrum of Activity:

- Broad Spectrum: affects both gram positive and gram negative bacteria.
- Narrow Spectrum: affects only one group, either gram positive or gram negative bacteria.

Antimicrobial Agents

Selective Toxicity: the agent's ability to kill or inhibit the growth of a microorganism without harming the host cell.

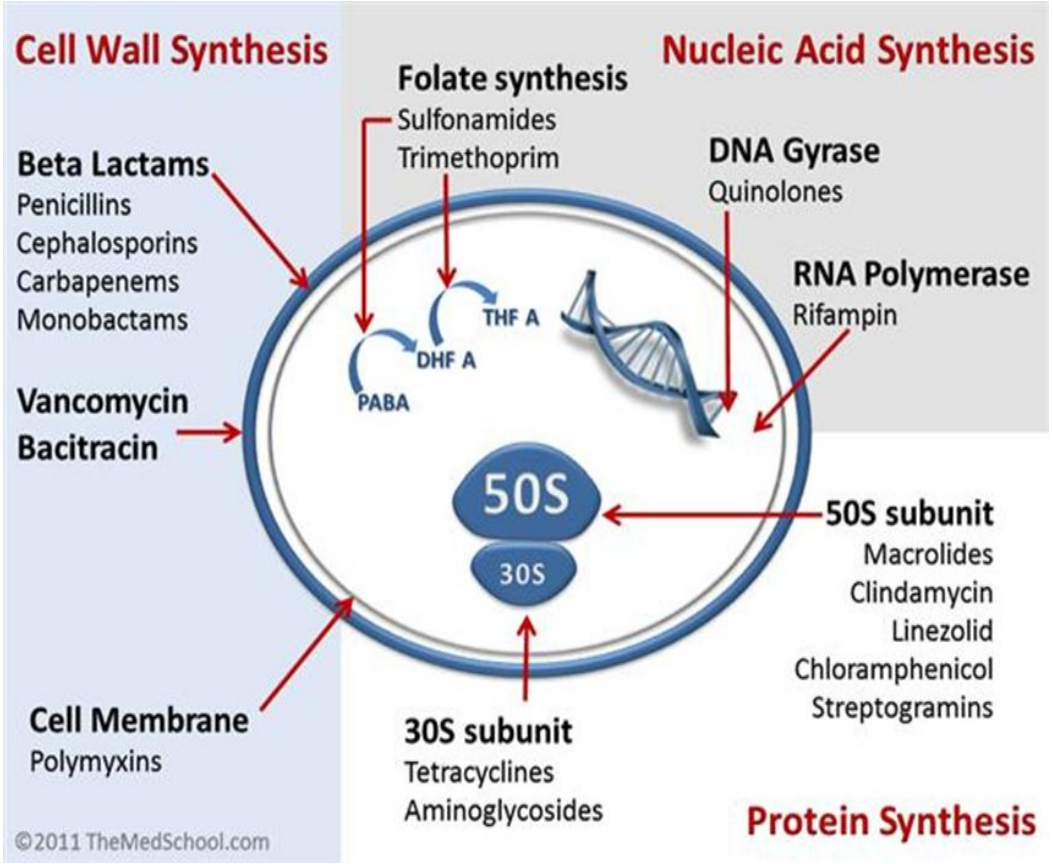
Therapeutic Index: the ratio of the *toxic dose to humans* and the *therapeutic (effective) dose to the bacteria* (the higher the therapeutic index, the safer it is for human use).

Examples:

- penicillin: high therapeutic index.
- Aminoglycosides: low therapeutic index.
- Polymyxin B: lowest therapeutic index (very toxic when given systemically).

Mechanisms of Action of Antimicrobial Agents

1) Inhibition of cell wall synthesis.
2) Inhibition of protein synthesis.
3) Inhibition of nucleic acid synthesis.
4) Alteration of cell membrane.
5) Anti-metabolite OR competitive antagonism.



Antimicrobials that inhibit cell wall synthesis

1- β-Lactam Antimicrobial Agents (most important and most used).

•Contains β-Lactam rings & organic acid

•Bactericidal

•Natural & semi-synthetic

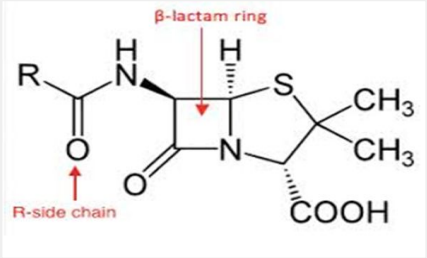
•Binds to PBP (Penicillin Binding Protein), interferes with trans-peptide reaction (leads to cell wall destruction)

•Toxicity; mainly:

- Hypersensitivity (type 1)
- Anaphylaxis
- Diarrhea

•They include:

- Penicillins
- Cephalosporins
- Carbapenems
- Monobactam (Aztreonam)
- B-Lactamase inhibitors



2- Vancomycin (Teicoplanin)

•Glycopeptides

•Bactericidal

•Acts on gram+ bacteria only (narrow spectrum).

•Inhibit cell wall synthesis.

•Given by injection only.

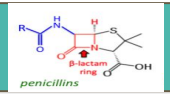
•Used for:

- MRSA (Methicillin-resistant staphylococcus aureus).
- S.epidermidis
- Pseudomembranous colitis

•Side effects:

- Nephrotoxicity
- Ototoxicity
- Red Man syndrome
- Phlebitis

B-Lactam Antibiotics



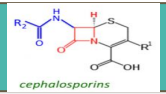
Penicillins

1.Benzyl Penicillin:
- Acts mainly on gram+ bacteria
- e.g.: Penicillin V, Procaine penicillin, & Benzathine penicillin

2.Isoxazolyl Penicillin:
- Effective for staphylococcus aureus
- e.g.: Cloxacillin

3.Amino-penicillins:
- Effective for enterobacteria
- e.g.: Ampicillin (acts on gram+, gram-, & anaerobes)

4.Acylaminopenicillin:
- Effective for Pseudomonas
- e.g.: Piperacillin & Mezlocillin



Cephalosporins

1.First generation: gram+ and some gram-
- ❖ Cefazolin
- ❖ Ceohalexine

2.Second generation: gram+ and some gram-
- ❖ Cefuroxime
- ❖ Cephamycin (Cefoxitin; acts on anaerobes)

3.Third generation (expanded spectrum): gram- & some gram+
- ❖ Ceftriaxone
- ❖ Ceftazidime (pseudomonas)

4.Fourth generation: gram- & some gram+
- ❖ Cefepime
- ❖ Cefexime

5.Fifth generation: multi-resistant gram+ & gram- bacteria
- ❖ Ceftobiprole

β-Lactamase Inhibitors

β-Lactams with no antibacterial activity. (added to antibiotics)

Irreversibly bind to β-Lactamase enzyme.

Examples: Clavulanic acid, Sulbactam, & Tazobactam.

Effective on staph. Penicillinases & broad spectrum β-lactamases.

Examples of antibiotics used with inhibitors: Amoxicillin/Clavulanic acid, Ticarcillin/Clavulanic acid, & Piperacillin/Tazobactam.

β-Lactamase is an enzyme in bacteria that breaks β-lactam rings in antibiotics (like penicillin). β-lactamase inhibitors are used to inhibit this enzyme, and allows antibiotics with β-lactam rings to work on bacteria.

Carbapenems

β-Lactams.

Cover gram+, gram-, & anaerobes (broad spectrum)

Restricted to critically ill patients or patients infected with multi-resistant organisms.

Given by injection.

Ex: Imipenem & Meropenem.

Antibiotics that alter cell membranes

Polymyxin B	Colistin (polymyxin E)
•Peptide •Active against gram- bacteria only •Only used locally due to serious nephrotoxicity	•Bactericidal •Active against gram- bacteria only •Causes nephrotoxicity •Used for treatment of multi-resistant organisms (MRO) such as Pseudomonas and Acinetobacter infections

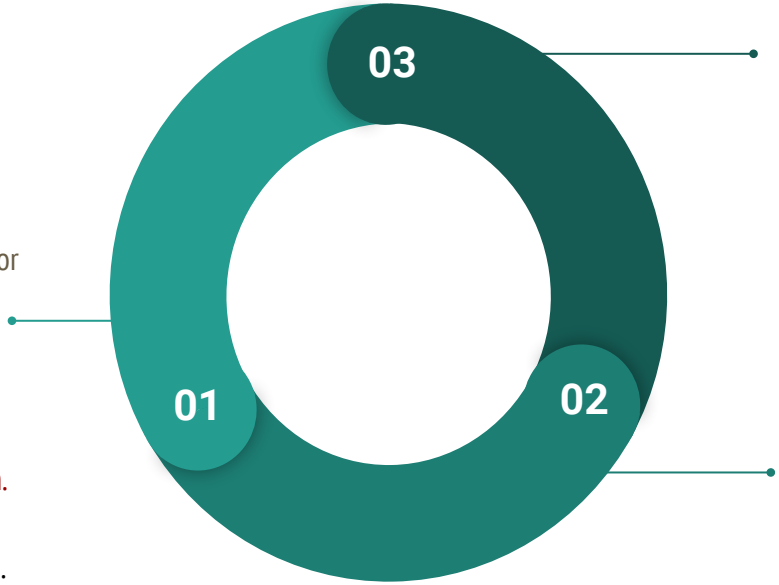
Antibiotics that inhibit protein synthesis

Aminoglycosides (binds to 30S ribosomal subunit)	Tetracyclines (binds to 30S ribosomal subunit)	Chloramphenicol (binds to 50s ribosomal subunit)	Macrolides (binds to 50s ribosomal subunit)	Oxazolidinones (binds to 50s ribosomal subunit
•Bactericidal •Acts only on gram (-) bacteria •Streptococci & anaerobes are naturally resistant •Examples: ❖ Gentamicin ❖ Amikacin ❖ Neomycin •Given by injection •Nephrotoxic & Ototoxic-dose related	•Bacteriostatic •Broad spectrum •Oral absorption •Effective against intracellular organisms, example: ❖ Mycoplasma ❖ Chlamydia ❖ Brucella ❖ V.cholera ❖ Nocardia •Classes: ❖ Short acting: tetracycline ❖ Long acting: minocycline, doxycycline (good CSF penetration) ❖ New tetracycline: tigecycline (MRSA, MSSA, some gram- bacteria & anaerobes) •Side effects: teeth discoloration & GIT disturbance •Should not be given to pregnant women or children under 7 years	•Broad spectrum (effective against all bacteria that cause meningitis) •Bactericidal or bacteriostatic •Affects bone marrow cells and causes aplastic anemia •Limited use: used for severe infections not responding to treatment by other antimicrobials, & also for Rickettsial diseases •Can be applied topically for eye & ear infections	•Types: erythromycin (macrolide) & clindamycin (lincosamide) •Bacteriostatic •Macrolides act on: Legionella, Canylobacter, gram- & gram+ infections for patients allergic to penicillins and cephalosporins •Clindamycin acts on staph, strept, & anaerobe •Causes GIT disturbance & Pseudomembranous colitis (mainly clindamycin) •New types: Azithromycin & clarithromycin (less side effects, better penetration, & longer half-life)	•Linezolid •Inhibits protein synthesis •Used to treat multi-resistant gram+ bacterial infections •Common side effects: -Thrombocytopenia -Diarrhea

ANTIMICROBIALS THAT ACT ON NUCLEIC ACID

QUINOLONES

• Synthetic, bactericidal, inhibit DNA Gyrase and /or Topoisomerase.
• **Generations:**
first generation: Nalidexic acid –locally acting
Second generation: Fluoroquinolones eg. Ciprofloxacin, Norfloxacin, Ofloxacin,Levofloxacin.
Third generation: Sparfloxacin, Gatifloxacin
Fourth generation: Moxifloxacin, Trovafloxacin.
• **Side effects:** affects the cartilages (mainly in animals) & the heart Should be used with caution for patients under 18 year and pregnancy.



Metronidazole

• A Nitroimidazole active on anaerobic bacteria and parasites.
• Used for the treatment of infections due to : Bacteroides fragilis (bacteria) , Trichomonas vaginalis , amoebiasis and giardiasis (parasites).
• **Side effects:** Causes DNA breakage.

RIFAMPICIN

• Semi-synthetic, bactericidal , acts on Gram positive bacteria and selected Gram negative bacteria.
• Reserved for Tuberculosis
• Resistance develops quickly. Must be used in combination with other antimicrobial agent.
• **Side effects:** Causes discoloration of body fluids & hepatotoxicity.

Summary TN

Side Effect:

Target	*Inhibition Of cell wall*						Inhibition of cell membrane (Bactericidal)	
	β=lactams (Bactericidal)					*Glycolipid* Bactericidal Using for MRSA		
Spectrum of Activity	*Penicillin*		*Cephalosporins*	*β=lactamase*	*Carbapenem*			
+ve Gram	Benzyl- penicillin Isoxazolyl- penicillin : s.aureus Amino- penicillin : Enterobacteria	Side Effect : 1) Allergy (common). 2) Anaphylaxis (serious). 3) Diarrhea	1st generation : +ve & some -ve 2nd generation: +ve & some -ve, &* 3rd generation : -ve & some +ve 4th generation : -ve & some +ve	Broad Spectrum e.g. : amoxicillin/ clavulanic acid	Broad Spectrum Restricted to critically ill patients	Vancomycin nephrotoxicity & ototoxicity, phlebitis, Red man syndrome		
-ve Gram	Acylamino- penicillin : Pseudomonas						Polymyxin B and Colistin (polymyxin E)	Nephrotoxicity
Anaerobic			*2nd generation: e.g. : cefoxitin					
Parasite								

Summary cont.

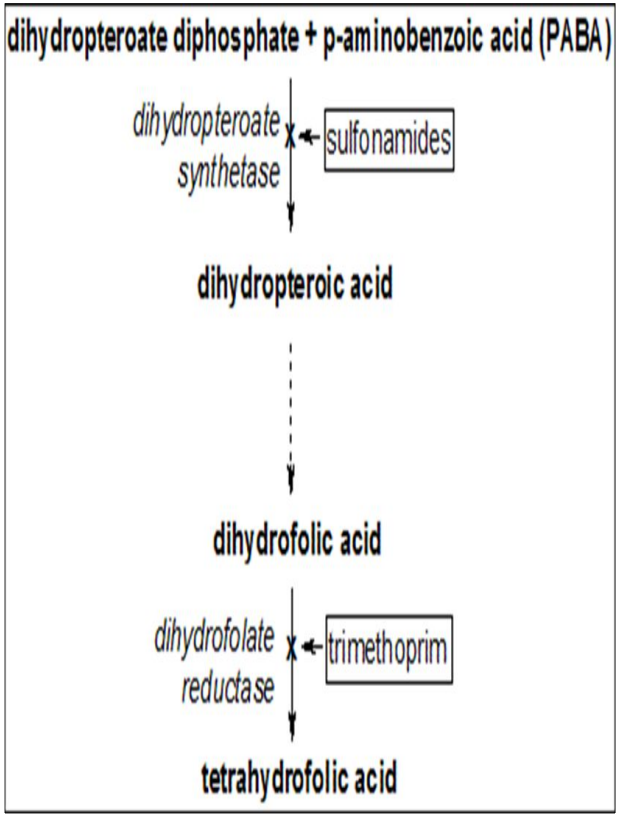
TN

Side Effect:

Target	Inhibition Of protein synthesis						Act on nucleic acid All examples affects DNA		
Spectrum of Activity	AminoGlycoside 30s ribosomal sub Bactericidal E.g. Gentamicin	TetraCyclin 30s ribosomal sub Bacterostatic	Chloramphenicol 50s ribosomal sub Bactericidal (topically)	Macrolides/Lincosamides 50s ribosomal sub Both Bacterostatic Macrolides e.g. : (Erythromycin)	Lincosamides e.g. : (Clindamycin)	Oxazo-lidonones E.g. (Linezoid)	Rifampicin Bactericidal	Quino-lones Bactericidal	
+ve Gram		Broad spectrum + Intracellular organism	Broad spectrum	Broad spectrum Used for patients allergic to penicillins and cephalosporins	Affects Staphylococci & streptococci	Multi resistant +ve	Reserved for Tuber-culosis (TB) Resistance develops quickly	Broad spectrum	
-ve Gram	Act on gram –ve Streptococci & anaerobes are naturally Resistance.								
Anaerobic					Affects Anaerobes				Metroni-dazole, S.E:Causes DNA breakage
Parasite									
Side Effect:	Nephrotoxicity & Ototoxicity	Teeth discoloration + Not used for children Or pregnancy	Affect bone marrow and may cause a plastic anemia			Thrombocytopenia & diarrhea	Affects body fluids colors+ Hepatotoxcity	Affects cartilage + pregnancy & heart	

ANTIMETABOLITES (folate inhibitors)

- ★ Trimethoprim-Sulfamethoxazole (TMP-SMX)
- ★ *Commonly used in Combination of TMP-SMX .*
- ★ Block sequential steps in folic acid synthesis
- ★ Effective of infections caused by different organisms ,eg. *Nocardia, Chlamydia, Protozoa & Pneumocystis caranii* infections
- ★ Used for the treatment of upper & lower respiratory tract infections , otitis media, sinusitis & infectious diarrhea.
- ★ Side effects: GIT, hepatitis , bone marrow depression & hypersensitivity



Anti-tuberculosis agents

First Line agents :

A combination of 3 or 4 drugs used for 4-6 months.
eg. INH+ Rifampicin + Ethambutol + Pyrazinamide for 2 months then continue INH + Rfampicin for 4 months.

- **Isoniazid (INH):**	- **Rifampicin.**	- **Ethambutol:**	**- Pyrazinamide:**
-Bactericidal. -Inhibits mycolic acid synthesis. -Affects mycobacteria at different sites of lung tissue, -Used for the treatment & prophylaxis of tuberculosis. -Can cause peripheral neuritis (pyridoxine (vitamin B6) added in certain patients) and hepatitis.		-Affects cell wall synthesis. -Optic neuritis.	-Exact mechanism unknown. -Hepatitis & arthralgia.

Second line agents

Used for resistant cases or cases not responding to first line drugs.

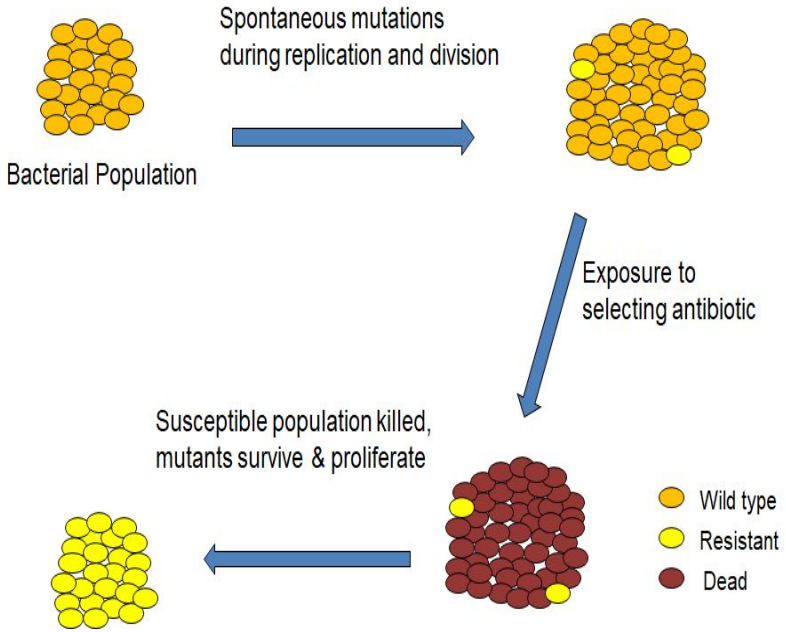
-Streptomycin	- Para amino salicylic acid (PASA).	- Cycloserine	- Capreomycin

ANTIBIOTIC RESISTANCE IN BACTERIA

- ★ Resistance develops due indiscriminate use of antimicrobial agents.
- ★ This creates a selective advantage for bacteria to grow in the presence of antibiotic.
- ★ **Type of resistance:**

01	**Primary (Innate) resistance :**	• Eg. *Streptococcus* & anaerobes are naturally resistant to Gentamicin.
02	**Secondary (acquired) resistance :**	★ Mutation ★ Gene transfer (e.g. plasmid mediated or through transposons)

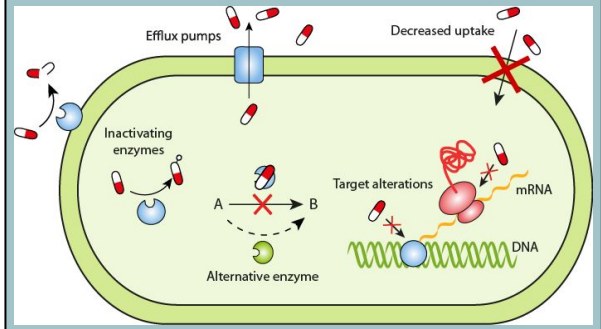
Antimicrobial Selection of Resistance



Antibiotic resistance in bacteria cont.

Mechanisms of resistance

1. Decreased permeability to antimicrobial agent (like a mutation in the porins in gram negative bacteria)
2. Alteration of antibiotic binding sites.
3. Inactivation by enzymes E.g Beta-lactamase &aminoglycoside)
4. Active transport out (efflux pumps) of cells



Principles of antimicrobial therapy

- ★ INDICATION
- ★ CHOICE OF DRUG
- ★ ROUTE
- ★ DOSAGE
- ★ DURATION
- ★ DISTRIBUTION
- ★ EXCRETION
- ★ TOXICITY
- ★ COMBINATION USE AS IN TUBERCULOSIS

★ Prophylaxis (to prevent recurrence of infection)

A-SHORT TERM(PROPHYLAXIS) :

- MENINGITIS

B- LONG TERM (PROPHYLAXIS):

Tuberculosis,Recurrent urinary tract infections ,Rheumatic fever

Criteria for ideal antimicrobial agent

- ★ SELECTIVE TOXICITY
- ★ NO HYPERSENSITIVITY
- ★ PENETERATE TISSUES QUICKLY
- ★ RESISTANCE NOT DEVELOP QUICKLY
- ★ NO EFFECT ON NORMAL FLORA
- ★ BROAD

MCQs:

Q1- which one of the following is an example of beta-lactamase inhibitor?

A) Amoxicillin
B)Clavulanic Acid
C) ticarcillin
D) Penicillin

Q2-Which of the following best describes BACTERIOSTATIC:

A)Antimicrobial agent that kills the bacteria
B) Antimicrobial agent that prevents multiplication of the bacteria
C)Antimicrobial agent that affects only selected organisms or group of bacteria (G+VE,or G-VE).
D)None

Q3- Broad spectrum antibiotic kills:

A) Gram positive bacteria
B) Gram nigative bacteria
C) Both

Q4- Which of the following is a side effect of Linezolid:

A)Thrombocytopenia.
B)Diarrhea.
C)Nephrotoxicity
D) A & B

Q5- Which one of the following results in teeth discoloration?

A)Clavulanic Acid
B) Tetracyclines
C)Penicillin
D) Amoxicillin

SAQ:

1- Define SELECTIVE TOXICITY:

ANS: is the The ability to kill or inhibit the growth of a microorganism without harming the host cells.

2-What are the side effects of VANCOMYCIN:

ANS: nephrotoxicity & ototoxicity, phlebitis, Red man syndrome

Take Home Messages:

- ★ Antibiotics can do harm, resistance can develope so must be used judiciously.
- ★ Antibiotics potentiate the function of human immune system to fight microbes.
- ★ Physicians must know the pharmacokinetics, spectrum of activity and toxicity of antimicrobial agents to make best use antibiotics.

Q1/B Q2/B Q3/C Q4/D Q5/B

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