ANTIMICROBIAL AGENTS: GENERAL CONSIDERATIONS

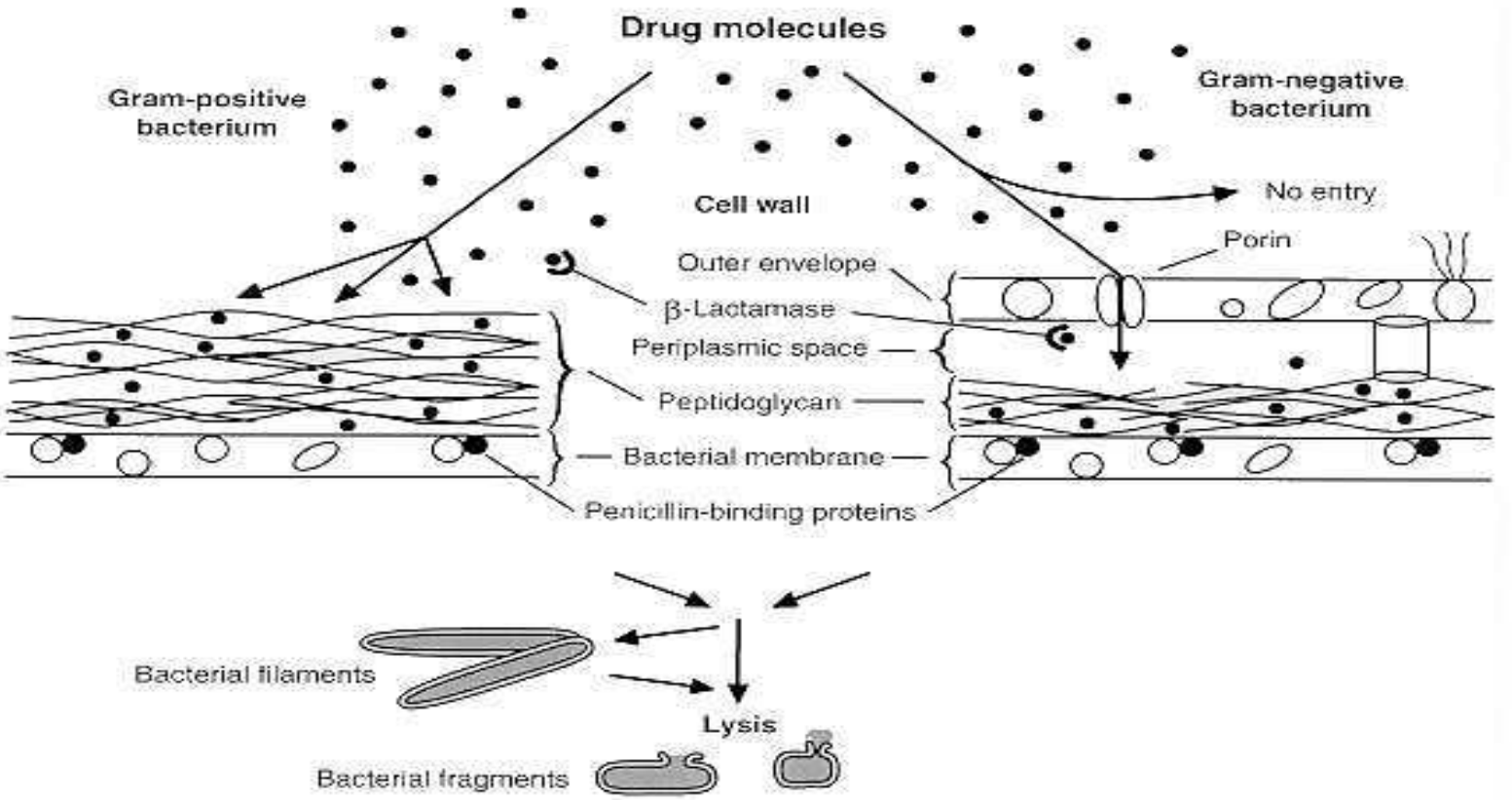
- ANTIBIOTICS /AMAs
- Bacteriostatic/bactericidal
- CLASSIFICATION & MOA
- ANTIMICROBIAL RESISTANCE
- SELECTION OF AN ANTIMICROBIAL AGENT
- TOXICTY OF AMAs
- THERAPY WITH COMBINED AMAs
- PROPHYLAXIS OF INFECTION WITH AMAs
- MISUSE OF AMAs

- Chemotherapy: Paul Ehrlich
- “treatment of systemic/topical infection with drugs that have selective toxicity for invading pathogens without harming the host cells.”

ANTIMICROBIAL AGENTS:CLASSIFICATION & MOA

- INHIBITION OF BACTERIAL CELL WALL SYNTHESIS
- Gm.+ve bact.cell wall contains peptidoglycan & techoic acid & may /maynot be surrounded by a protein polysacch envelope. Gm –ve bact.cell wall contains peptidoglycan, and an outer envelope of lipopolysaccaride, phospholipid & protein.
- Peptidoglycan layer - critical site of attack of anti-cell wall agents eg Beta lactams (Pn, CS, Monobactams) and glycopeptides(Vanco, teicoplanin).

Difference in str. of gm+ve & gm –ve bacteria



•Antibiotics that Affect the Function Cytoplasmic Membranes

Cytoplasmic membrane : diffusion barrier for water, ions, nutrients, and transport systems.

- **Polymyxin B** and P**olymyxin E : cationic detergents**
- Inhibit Gram-ve bacteria having negatively charged lipids at the surface. They competitively displace Mg2+ or Ca2+ from negatively charged phosphate groups on membrane lipids.

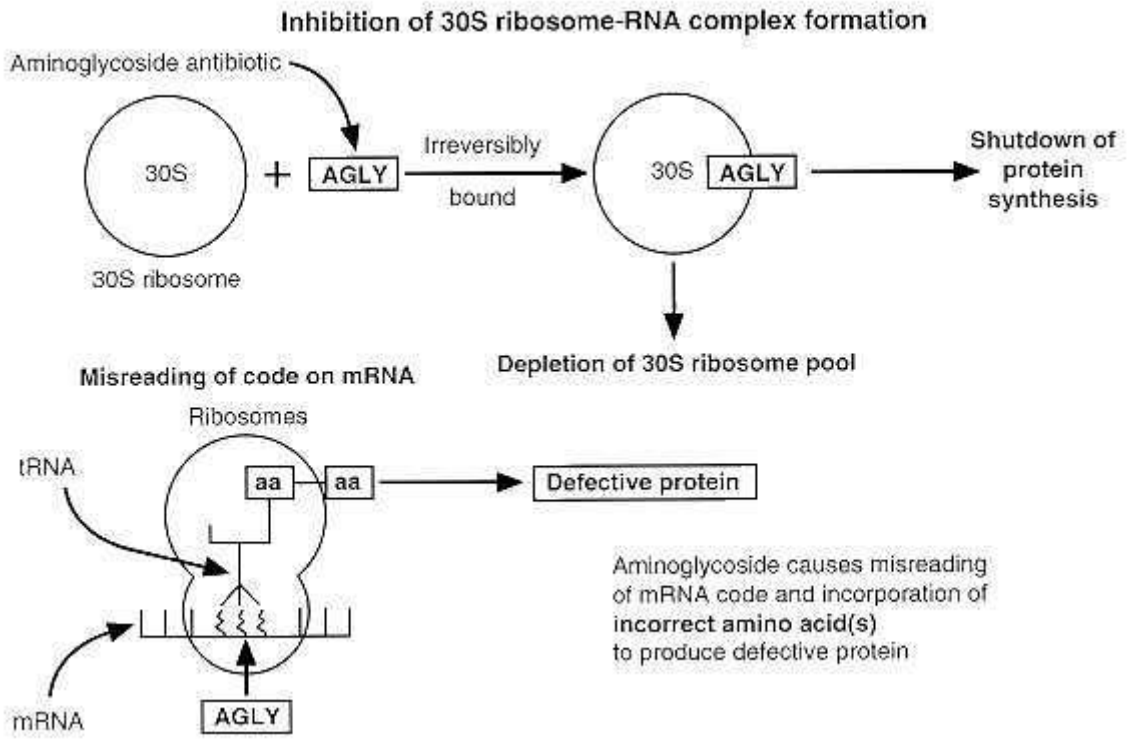
- disorganize membrane permeability - nucleic acids and cations leak out - cell dies.
- Polymixins :Not used as systemic agents : toxic for kidneys,CNS

- **Gramicidins** also membrane-active antibiotics , act by producing aqueous pores in the membranes, are also used only topically.

Antimicrobials inhibiting ribosomal protein synthesis

- Aminoglycosides :bind to a specific protein in 30S ribosomal subunit and causes the ribosome to misread the genetic code : Bactericidal
- Tetracyclines also bind 30S of bacterial ribosome. Tetracycline binding is transient --*bacteriostatic.*

MOA-AGs


Inhibition of 30S ribosome-RNA complex formation
Aminoglycoside antibiotic
30S
AGLY
Irreversibly
bound
30S
AGLY
Shutdown of
protein
synthesis
30S ribosome
Depletion of 30S ribosome pool
Misreading of code on mRNA
Ribosomes
tRNA
aa
aa
Defective protein
Aminoglycoside causes misreading
of mRNA code and incorporation of
incorrect amino acid(s)
to produce defective protein
mRNA
AGLY

Ribosomal Inhibitors (contd---)

- 3 classes AMAs that inhibit **50S ribosomal SU**

- **Chloramphenicol :** bacteriostatic agent, inhibits peptide bond formation by binding to a peptidyltransferase enzyme on the 50S ribosome.

- **Macrolides** are large lactone ring compounds, bind to 50S ribosomes and impair a peptidyltransferase reaction or translocation, or both.

- **Lincocamides eg. clindamycin,** have a similar site of activity. Both macrolides and lincosamides are generally bacteriostatic, inhibiting only the formation of new peptide chains.

Antimicrobials suppressing DNA synthesis

- **Interference with Nucleotide Synthesis**

  Flucytosine an antifungal agent - converted in the fungal cell to 5-fluorouracil:h inhibits thymidylate synthetase resulting in impaired DNA synthesis.

- **Acyclovir** a nucleoside analog : converted to a triphosphate : inhibits thymidine kinase & DNA polymerase of herpes viruses.

- **Zidovudine (AZT**) inhibits HIV by interfering with viral RNA-dependent DNA polymerase (reverse transcriptase).

DNA synthesis inhib.(contd…)

- **Inhibition of DNA-Directed RNA Polymerase**
- Rifamycins inhibit DNA-directed RNA polymerase. **Rifampicin** binds to a subunit of RNA polymerase and interferes specifically with the initiation process.
- **Direct damage to DNA and it's functioning**:
- Many **anticancer** drugs make a covalent bonding with bases of DNA .
- **Metronidazole** also damages protozoal/anaerobe DNA by direct action.

DNA Synth.inhib(contd…)

- DNA gyrase(Gm –ve) and topoisomerase IV (Gm +ve)maintain an optimum supercoiling state of DNA in the cell.
- DNA gyrase - essential for relieving torsional strain during replication of circular chromosomes in bacteria. Composed of two A and two B subunits.
- **Nalidixic acid** and FQ like **Ciprofloxacin block** the cutting and resealing activity of DNA gyrase and topo IV

BACTERIAL RESISTANCE TO AMAs

- Unresonsiveness of a microorg. to an AMA after its repeated use.
- A) Intrinsic B)Acquired: a)genetic mech. b)biochem
- B) Genetic: Chromosomal mutations –mycobacteria , MRSA agnst quinolones, rifampin ,STM,.
  Extra chromosomal ;thru plasmids : m. imp, r- genes
  Transduction- staph. resist. to Pn, tetras, chlormph
  Transformation Pn resist.pneumococci –altered PBP
  Conjugation v imp. mode –MDR .Common in Gm-ve bacilli – vanco resist. Enterococci, multple resist.Enterob, MRSA, MDR TB ,

Biochemical mech. of antimicrobial resistance

- **Drug does not reach it's target**
- Porin channels in gm-ve bact. absent/mutated/lost –slow rate of drug entry or prevent entry >AG, ampicilin
- Inhibition of active transp. > AGs
- Efflux pumps >beta lactams , tetras
- **Inactivation of drug by enzymes**
- Beta lactamases , AG modifying enz., acetylransferases:chloramp.
- Failure of bact. Cell to convert inactive drug to active:resist to INH

Resist.(contd….)

- **<u>Alteration of target site</u>**
- Ribosomal point mutations:tetras, macrolides, clinda
- Altered DNA gyrase & topoisomerase:FQ
- Modified PBP: pneumococci
-
- **<u>Use of alternative pathways for metab/growth req</u>:** overprod.of PABA: sulphonamide resist.

TABLE 11-4 Mechanisms to Reduce Antibiotic Resistance

1. Control, reduce, or cycle antibiotic usage
2. Improve hygiene in hospitals and among hospital personnel and reduce movement of patients to eliminate the dissemination of resistant organisms within hospitals
3. Discover or develop new antibiotics
4. Modify existing antibiotics chemically to produce compounds inert to known mechanisms of resistance
5. Develop inhibitors of antibiotic-modifying enzymes
6. Define agents that would "cure" resistance plasmids

Selection of an AMA

- AMAs used in 3 gen. ways *1)Empirical therapy :*
- *2) Definitive therapy*
- *3)Prophylactic therapy*
- Narrow spectrum /broad spectrum
- Nosocomial /community acquired
- Antibiogram

Selection of an AMA…

- **Susceptibility of infecting microorganisms**.
- Testing for microbial sensitivity to AMA: Disc diffusion, agar or broth dilution tests & automated tests:
- MIC :lowest conc. Of AMA that prevents the growth of microorg after a 24 hr incuabation period wuth a std inoculum

Selection of an AMA…

- **PK factors**: Location of inf.-dictates drug & route of adm., eg CSF inf.,
- Status of pt mech.for elimin.of drug: renal , hepatic insuff.
- Drugs CI / to be used with caution

AMA selection(contd….)

- Host factors:
- A)Host defense mech.- Bstatic /Bcidal eg bact.
- Endocarditis & meningitis – Bcidal agent req, also in Neutropenic pts, AIDS
-
- B)Local factors : Pus reduce act of AMAs: AGs ineffective in abscess d/t anaerobic cond. But NFT, Tetra more effective

Host factors…

- Presence of Foreign body in infected site: success of AMA therapy ↓.
- Prosthetic mat.eg. Prosthetic valves, vascular grafts etc perceived as FB by phagocytes.>high relapse & failure rate---Bcidal high dose

Selection of AMA contd-----

- Intracellular pathogens eg Salmonella, Brucella, M.tubercolosis, toxoplasma – FQ,INH,RMP, Cotrimox

- C) Age: Neonates: grey-baby synd, kernicterus,
- Tetras, FQs CI in pediatric pt. ;
- Elderly patient

- D) Genetic factors: G6PD def.

- E) Pregnancy: STM hearing loss in child, Tetras affect bone & teeth of fetus, ac. Fatty necrosis of liver, renal damage of mother

- F) Drug allergy

G) Disorders of CNS :Pn G

Selection of AMA contd-----Antimicrobial PD

- Bactericidal agents exhibit Conc-dependant killing (CDK) or Time-dependant killing (TDK)
- Post –antibiotic effect (PAE): Persistent suppression of bact growth after limited exp to an AMA.
- AG & Quinolones have CD PAEs ,
- OD dosing of Aminoglycosides

Therapy with combined AMAs

- Combination of 2 or more AMAs m/b synergistic, additive or antagonistic. **Synergistic** :Inhibition of growth by combi at conc ≤25% of MIC of each drug alone. **Additive** : if 50% of MIC of each drug is reqd to produce inhibition of growth. **Antagonistic**: if > 50%of MIC of each is reqd.
- Combi of Bstatic & bcidal AMAs is usually antagonistic
- Combi of 2 Bcidal AMAs is gen. synergistic

Combined AMAs (contd…)

- Indications for clinical use of combi of AMAs
  1) **Empirical therapy** of infection of unknown cause
- 2) treatment of **polymicrobial infections**
- **3)Enhancement of antibacterial** act. in specific infec. eg treatment with Pn & Gentamicin for enterococal & streptococcal endocarditis, Pseudomonas infections – **synergistic**
- 4)**Prevention** of emergence of **resistant microorganisms eg** TB, Leprosy, HIV

Combined AMAs (contd….)

- **Disadvantages**
- ↑toxicity
- Selection of MDR microorganisms
- ↑ cost to pt
- Antagonism if cidal + static

Prophylaxis of infection with AMAs

- Highly effective in some clinical settings while without value in others. Controversial in many sitn.
- *If a single, effective ,nontoxic drug is used to prevent inf by a specific microorg or to eradicate an early inf, then chemoprophylaxis is freq successful*.
- May be used to protect healthy persons eg RMP to prevent meningo meningitis, co-trimox for recurr UTI

Chemoprophylaxis…

- Used to prevent inf. In organ transp/ Ca chemo
- Used for pt with valvular/str. lesions predisp to endocarditis undergoing surgical/dental proced. Causing high incid of bacteremia

Chemoprophylaxis (contd….)

- Most extensive use of chemoproph is to prevent wound inf. after various surgical proced. Guidelines exist.
- Imp factors : 1) Timing: AMA act. Must be present at wound site at time of it's closure. 2) AMA must be active agnst most likely contaminating org- CS used commonly 3) use beyond 24 hrs usually not necessary.

Chemoprophylaxis (contd….)

- Use justified in dirty & contaminated surg proced.or insertion of prosthetic implants
-
- Cefazolin 1 gm IV at induc of anaesthesia m.commonly used

Superinfections

- *Appearance of bacteriologal and clinical evidence of a new inf. during the chemoth. of a primary one*.

- Broad spectrum AMAs cause greater alteration in normal microflora.

- Narrow spectrum AMAs: safest

Misuse of AMAs

- Treatment of untreatable infections
- Therapy of PUO
- Improper dosage
- Inappropriate reliance on chemotherapy alone
- Lack of adequate bacteriological information.