ANTIMICROBIAL AGENTS: GENERAL CONSIDERATIONS

- ANTIBIOTICS /AMAs
- Bacteriostatic/bactericidal
- CLASSIFICATION & MOA
- ANTIMICROBIAL RESISTANCE
- SELECTION OF AN ANTIMICROBIAL AGENT
- TOXICITY 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/may not be surrounded by a protein polysacch envelope. Gm –ve bact. cell wall contains peptidoglycan, and an outer envelope of lipopolysaccharide, 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 Polymyxin 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 → AGLY → Irreversibly bound

AGLY → Depletion of 30S ribosome pool

AGLY → Shutdown of protein synthesis

Misreading of code on mRNA

Ribosomes

AGLY

Aminoglycoside causes misreading of mRNA code and incorporation of incorrect amino acid(s) to produce defective protein

Defective protein

mRNA

aa

Aminoacyl-tRNA

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: 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 its 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.


- **Nalidixic acid** and FQ like **Ciprofloxacin** block the cutting and resealing activity of DNA gyrase and topo IV.
BACTERIAL RESISTANCE TO AMAs

- Unresponsiveness 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 against quinolones, rifampin, STM.
Extra chromosomal: through plasmids: m. imp, r- genes

Transduction: staph. resist. to Pn, tetras, chlormph
Transformation: Pn resist. pneumococci – altered PBP
Conjugation: very important mode – MDR. Common in Gm-ve bacilli – vanco resist. Enterococci, multiple 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., acetyltransferases: chloramp.
- Failure of bact. Cell to convert inactive drug to active: resist to INH
Resist. (contd. . .)

- **Alteration of target site**
- Ribosomal point mutations: tetras, macrolides, clinda
- Altered DNA gyrase & topoisomerase: FQ
- Modified PBP: pneumococci

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<th>Mechanisms to Reduce Antibiotic Resistance</th>
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<td>1.</td>
<td>Control, reduce, or cycle antibiotic usage</td>
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<td>2.</td>
<td>Improve hygiene in hospitals and among hospital personnel and reduce movement of patients to eliminate the dissemination of resistant organisms within hospitals</td>
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<td>3.</td>
<td>Discover or develop new antibiotics</td>
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<td>4.</td>
<td>Modify existing antibiotics chemically to produce compounds next to known mechanisms of resistance</td>
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<td>5.</td>
<td>Develop inhibitors of antibiotic-modifying enzymes</td>
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<td>6.</td>
<td>Define agents that would “cure” resistance plasmids</td>
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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 incubation 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** materials, e.g., 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. tuberculosis, 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 Concentration-dependent killing (CDK) or Time-dependent killing (TDK)
- Post-antibiotic effect (PAE): Persistent suppression of bacterium growth after limited exposure 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  \( \leq 25\% \) 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 predisposed 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 surgical procedures or insertion of prosthetic implants
- Cefazolin 1 gm IV at induction of anaesthesia is commonly used
Superinfections

- Appearance of bacteriological 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.