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DEPARTMENT OF PERIODONTICS



SEMINAR PRESENTATION ON – “ANTIBIOTICS”.

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INTRODUCTION

- Antibiotics are the greatest contribution of 20th century.
- These are the drugs designed to inhibit/kill the infecting organisms & to have no/minimal effect on recipient. This type of therapy is called chemotherapy.
- Selective microbial toxicity is due to action of drug the component of the microbes or metabolic process which are not found in host.

DEFINITION

- Antibiotics are the substances produced by microorganisms, which selectively suppress the growth of or kill other microorganisms at very low concentrations.

- Waksman.

HISTORY

- Mainly explained in 3 phases:
- Phase 1:
 - ❖ Period of empirical use:
 - Mouldy curd – Chinese on boils.
 - Cinchona bark – fever.
 - Chaulmoogra oil – Hindus in leprosy .
- Phase 2:
 - ❖ Ehrlich's phase of dyes & organometallic compounds(1890-1935):
 - ❖ Based on the idea of selective staining of microbes & he tried methylene blue, trypan red etc.
 - ❖ Coined the term "CHEMOTHERAPY".
- Phase 3:
 - ❖ Domagk (1935) demonstrated effects of prontosil, a sulfonamide dye in pyogenic infection.
 - ❖ Phenomenon of antibiosis – Pasteur in 1877.
 - ❖ Flemming (1929) found diffusible substance produced by penicillium mould that could destroy staphylococcus on culture plate.

- ❖ Chain & Florey followed these observations, which culminated in clinical use of penicillin in 1941.
- ❖ In 1940, Waksman & co – systemic search of antibiotics with actinomycetes as source & discovered streptomycin(1944).
- ❖ Nobel prizes.

CLASSIFICATION

- Based on chemical structure:
 - Sulfonamides & related drugs:
 - Sulfadiazines & others.
 - Sulfones – dapson.
 - Diaminopyridines:
 - trimethoprim, pyrimethamine.
 - Quinolones:
 - Nalidixic acid, norfloxacin, ciprofloxacin.
- β lactam antibiotics:
 - penicillins, cephalosporins, monobactams, carbapenems.
- Tetracyclines:
 - oxytetracyclines, doxycycline etc.
- Nitrobenzene derivatives:
 - Chloramphenicol.
- Aminoglycosides:
 - Streptomycin, gentamicin, neomycin, etc.
- Macrolides:
 - Erythromycin, clarithromycin, azithromycin, etc.
- Lincosamides:
 - Lincomycin, clindamycin.

- Polypeptide antibiotics:
 - Polymyxin-B, colistin, bacitracin, tyrotricin.
- Glycopeptides:
 - Vancomycin, teicoplanin.
- Oxazolidinone:
 - Linezolid.
- Nitrofurán derivatives:
 - Nitrofurantoin.
- Nicotinic acid derivatives:
 - Isoniazid, pyrazinamide, ethionamide.
- Glycopeptides:
 - Vancomycin, teicoplanin.
- Oxazolidinone:
 - Linezolid.
- Nitrofurán derivatives:
 - Nitrofurantoin.
- Nicotinic acid derivatives:
 - Isoniazid, pyrazinamide, ethionamide.
- Nitroimidazoles:
 - Metronidazole, tinidazole.
- Polyene antibiotics:
 - Nystatin, amphotericin-B, hamycin.
- Azole derivatives:
 - Miconazole, clotrimazole, ketoconazole, fluconazole.
- Others:

- rifampin, ethambutol, gresiofulvin, cycloserine, etc.
- Based on mechanism of action:
 - Inhibits cell wall synthesis:
 - Pencillins
 - Cephalosporins
 - Cycloserine
 - Vancomycin
 - Bacitracin
 - Cause leakage from cell membranes:
 - Polypeptides
 - Polyenes
 - Inhibit protein synthesis:
 - Tetracyclins - Clindamycin
 - Chloramphenicol -Linezolid
 - Erythromycin
- Misreading of m-RNA & affect permeability:
 - Aminoglycosides
- Inhibit DNA gyrase:
 - Fluoroquinolones
- Interference with DNA synthesis:
 - Acyclovir
 - Zidovudine
- Interference with intermediary metabolism:
 - Sulfonamides

- Ethambutol
- Diaminopyrimidines
- Interfere with DNA function:
 - rifampin, metronidazole
- Based on type of organisms against which primarily active:
 - Antibacterials:
 - Pencillins
 - Aminoglycosides
 - Erythromycin, etc
- Antifungals:
 - Griseofulvin
 - Amphotericin B
 - Ketaconazole, etc
- Antivirals:
 - Acyclovir
 - Amantadine
 - Zidovudine, etc.
- Antiprotozal:
 - Chloroquine
 - Pyrimethamine
 - Metronidazole
 - Diloxanide, etc.
- Anthelmintics:
 - Mebendazole
 - Pyrantel

- Niclosamide
- Diethyl carbamazine, etc.
- Based on spectrum of action:
 - Narrow spectrum: - Broad spectrum:

Pencillin G	Tetracyclines
Streptomycin	Chloramphenicol
erythromycin	
- Based on type of action:
 - Primarily bacteriostatic:
 - Sulfonamides
 - Tetracyclins
 - Chloramphenicol
 - Erythromycin
 - Ethambutol
 - Clindamycin
 - linezolid
 - Primarily bactericidal:
 - Pencillins -Ciprofloxacin
 - Aminoglycosides -Metronidazole
 - Polypeptides
 - Cephalosporins
 - Rifampin
 - Cotrimoxazole
 - Vancomycin

PROBLEMS ARISING WITH USE OF ANTIBIOTICS:

- Toxicity
- Hypersensitivity
- Drug resistance
- Super infection
- Nutritional deficiencies
- Masking of infections

CHOICE OF AN ANTIBIOTIC:

- The choice depends on the peculiarities of the
 - Patient
 - Infecting organism &
 - The drug

PATIENT FACTORS:

- Age
- Renal & hepatic functions
- Local factors
- Drug allergy
- Impaired host defence
- Pregnancy
- Genetic factors

ORGANISM RELATED CONSIDERATIONS:

- Each antibiotic has specific effect on limited organisms.
- Clinical diagnosis – 1st made, atleast tentatively & pathogen is guessed.
- Ideally, the identity & antimicrobial sensitivity have to done before antibiotic therapy.
- Being time consuming(atleast 48hrs), expensive & impractical for dental infections
- Most of which are acute in nature & treatment can't be delayed.

- Oral infections like periodontal abscess, periapical abscess, pulpal infections, periodontitis, ANUG etc caused by- bacteroides

anaerobes like- fusobacterium

porphyromonas

prevotella

veillonella

aerobic gram positive cocci

- Mixed infections- penicillin/ amoxicillin/some cephalosporins against anaerobes.
- Most dentist initiate empirical therapy with:

Amoxicillin+metronidazole

- Further, modification in therapy are made based on clinical response
- Hasty & arbitrary changes are to be avoided.
- In situations like ANUG, oral thrush- diagnosis itself indicates the pathogen & directs choice of drug.
- BACTERIAL SENSITIVITY TESTING:
 - Done by disc agar diffusion method using standard concentrations of antibiotics.
 - Broth cultures with break point concentration (demarcates sensitive & resistant strains) of antibiotics probably yield more reliable results.
- Minimal inhibitory concentration MIC:

the lowest concentration of the antibiotic required to prevent visible growth of a bacterium on a culture plate using serial dilutions of an antibiotic.

- Minimum bactericidal concentration MBC: of an antibiotic is determined by subculturing from tubes with no visible growth.
- If organism is killed no growth occurs, if not in antibiotic free medium it grows indicating its inhibition in parent culture.
- MBC is the concentration of an antibiotic which kills 99.9% of bacteria.

DRUG FACTORS:

- Spectrum of activity

- Type of activity
- Sensitivity of the organism
- Relative toxicity
- Pharmacokinetics
- Route of administration
- Evidence of clinical efficiency
- Cost

ANTIMICROBIAL PROPHYLAXIS IN DENTISTRY

- This is done for two distinct purposes:
 - a. Prevention of local wound infection
 - b. Prevention of distant infection

PROPHYLAXIS OF DENTAL WOUND INFECTIONS:

- Prevent from infection after tooth extraction.
- Sterile instruments, prevent cross infection, good surgical technique.
- Extensive instrumentation, bone cutting
- Procedures like insertion into bone or soft tissues(implants)
- Reconstructive surgeries.
- Diabetic, corticosteroid therapy, immuno-compromised conditions

PROPHYLAXIS FOR DISTANT INFECTIONS:

- Bacteraemia.
- Endocarditis
- Hip/knee joint replacement, orthopaedic prosthesis.
- Recent joint replacement, previous prosthetic joint infection etc
- Oral single dose 1 hr prior :
 - Amoxicillin- 2g(50 mg/kg)
 - Cephalexin- 2g(50mg/kg)

- Cefadroxil - 2g(50mg/kg)
- Clindamycin- 600mg(20mg/kg) if allergic to
- Azithromycin – 500mg(15mg/kg) pencillins.
- Parenteral single injection just before procedure:
 - Ampicillin- 2g(50mg/kg) i.m/i.v
 - Cefazolin- 1g(25mg/kg) i.v
 - Clindamycin- 600mg(20mg/kg) i.v if allergic to pencillin
- Prosthetic valve replacement
- h/o bacterial endocarditis in the past
- Operated under GA
- For above cases
- Gentamicin- 120mg(2mg/kg)i.m/i.v + amoxicillin
- Another dose of amoxicillin 500mg (12.5 mg/kg) repeated 6hrs after the procedure.
- Vancomycin 1g(20mg/kg) iv 2hrs + gentamicin 120mg (2mg/kg) i.m/i.v just before procedure allergic to pencillin.

β LACTAM ANTIBIOTICS:

- β lactam ring
- Pencillins, cephalosporins- most commonly used
- Monobactams & carbapenems- new addition

PENCILLINS

- 1st antibiotic (1941)
- P.notatum, present- p.chrysogenum.
- Classification:
 - Natural
 - Semi – synthetic

NATURAL PENCILLINS:

- Pencillin G
- Pencillin V

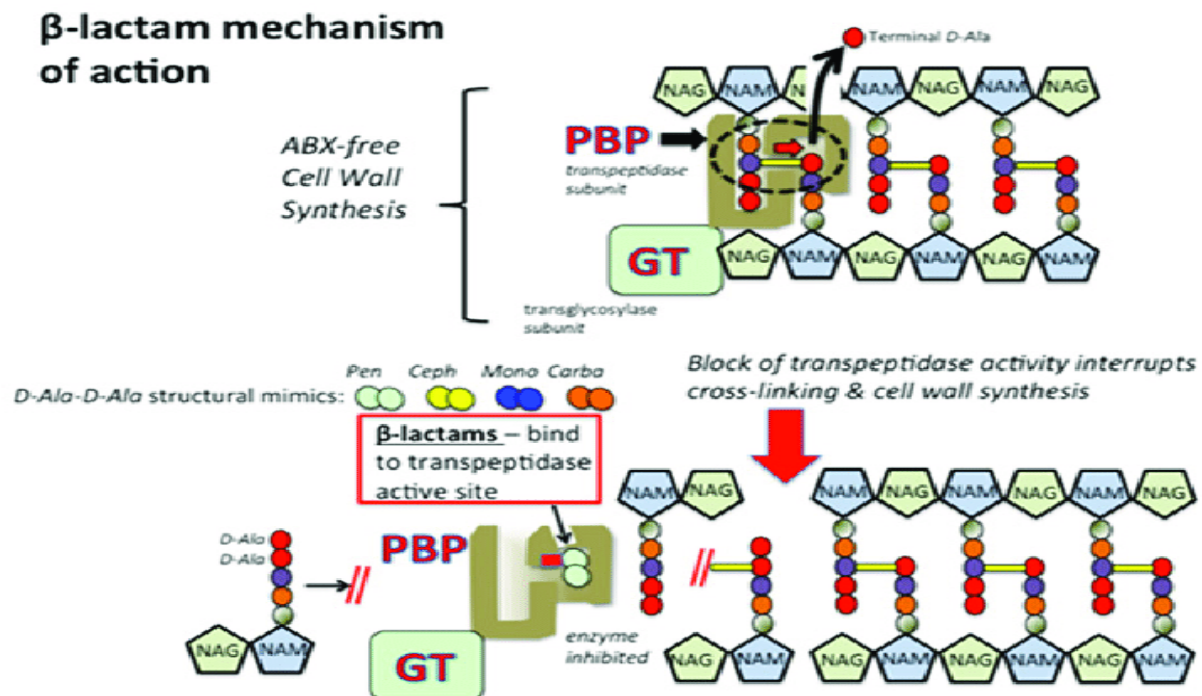
SEMI-SYNTHETIC PENCILLINS:

- Pencillinase resistant: methacillin, cloxacillin
- Extended spectrum:
 - Aminopencillins: ampicillin, bacampicillin, amoxicillin.
 - Carboxypencillins: carbenicillin, ticarcillin.
 - Ureidopencillins: piperacillin, mezlocillin.

β LACTAMASE INHIBITORS:

- Clavulanic acid
- Sulbactam
- Tazobactam

MECHANISM OF ACTION:



PENCILLIN G:

- Narrow spectrum
- Bacterial resistance– through penicillinase production & porin channel alteration
- Acid labile
- Excretion- glomerular filtration(10%)
tubular secretion(90%)
- $t_{1/2}$ – 30 min.
- Neonates – incompletely tubular secretion, so $t_{1/2}$ – longer
- Aged & renal failure pt. – excrete penicillin slowly.
- Tubular secretion is blocked by probenecid And it produces high, long lasting plasma concentrations
- Probenecid also reduces VOD of penicillins.

ADVERSE EFFECTS:

- Local irritancy, direct toxicity.
- Hypersensitivity.
- Super-infection.
- Jarisch – Herxheimer reaction.

USES IN DENTAL INFECTIONS:

- Effective in majority of common infections in dentistry.
- At ordinary doses used for
 - periodontal abscess,
 - pericoronitis,
 - acute suppurative pulpitis,
 - acute necrotising ulcerative gingivitis,
 - cellulitis, et.
- As prophylactic cover in dental procedures

- Presently their use is restricted.

SEMI-SYNTHETIC PENCILLINS:

- Chemically adding side chains or specific groups to parent molecule.
- Aims : to overcome
 - Poor oral efficacy.
 - Pencillinase susceptibility.
 - Narrow spectrum.
 - Hypersensitivity.

AMOXICILLIN:

- Semi-synthetic.
- Extended spectrum.
- Oral absorption- good, no food interference.
- Diarrhoea incidence is low.
- One of the most frequently used drug for infections like:
 - Aggressive periodontitis
 - Localised & generalized periodontitis
- 1st choice drug- prophylaxis.

β LACTAMASE INHIBITOR:

CLAVULANIC ACID:

- Streptomyces clavuligerus.
- Has β lactam ring, but no antibiotic activity.
- Inhibits β lactamases.
- Rapid oral absorption
- t_{1/2}- 1 hr
- Eliminated by glomerular filtration.

AMOXICILLIN – CLAVULANATE POTASSIUM:

- Combination – resistant to penicillinase
- Management of-
 - localised aggressive periodontitis or refractory periodontitis.
- Bueno et al, reported that augmentin halted alveolar bone loss in patients with periodontal disease.

CEPHALOSPORINS:

- Semi- synthetic, cephalosporin- C(cephalosporium).
- MOA similar to penicillins(at different proteins).

CLASSIFICATION OF CEPHALOSPORINS:

- 1st generation
 - **Parenteral:**
 - Cefuroxime.
 - **Oral:**
 - Cephalexin
 - Cephadrine
 - cephadroxil
- 2nd generation
 - **Parenteral:**
 - cefuroxime
 - **Oral:**
 - Cefaclor
 - Cefuroxime axetil
- 3rd generation:
 - **Parenteral:**
 - Cefotaxime

- Ceftriaxone
- Cefazidime
- Cefoperazone
- **Oral:**
 - Cefixime
 - Cefdinir
 - Cefibuten
 - Cefamet piroxil
- 4th generation
 - **Parenteral:**
 - Cefepime
 - cefpirome
- 5th generation
 - Ceftibiprole
 - Cefaroline

USES IN DENTAL INFECTIONS:

- No compelling indication, used as alternative to penicillin/amoxicillin in allergic pt. Or resistant to penicillins.
- Oral administration.
- 1st & 2nd gen. Cephalosporins which are active orally are used.
- Indirect action on anaerobes.
- Cefuroxime & cefaclor are active against anaerobes & preferred in dental infections.

SIDE EFFECTS:

- Rashes.
- Urticaria.
- Fever.

- GI upset.

TETRACYCLINES:

- Four cyclic rings.
- Source: soil actinomycetes.
- 1st introduced- chlortetracycline(1948).
- Broad spectrum antibiotics.

CLASSIFICATION:

- Short acting: $t_{1/2}$ = 6-10 hrs
 - Tetracycline.
 - Chlortetracycline.
 - Oxytetracycline.
- Intermediate acting: $t_{1/2}$ = 12-13 hrs
 - Demeclocycline.
 - Methacycline.
- Long acting: $t_{1/2}$ = 18-20 hrs
 - Doxycycline.
 - minocycline.
- Primarily bacteriostatic.
- Inhibit protein synthesis.
- Selective toxicity to microbes:
 - Sensitive- energy dependent active transport into cell.
 - Gram negative- porin channels.
 - More lipid soluble members- passive diffusion.

RESISTANCE:

- Slow & graded manner,
- Tetracycline concentrating mechanism- less effective or acquires- pump it out mechanism.
- Plasmid mediated protective protein synthesis, protect ribosomal sites.
- Tetracyclines have chelating property – Ca^{2+} , metal ions, iron preparations, antacids.
- Widely distributed in the body.
- Oral capsules are given 1/2 hr before or 2hrs before food.
- I.M not recommended- painful, poor absorption.
- They are concentrated in liver, spleen, gingival tissue.
- Binds to connective tissue of teeth & bones.
- Intracellularly- mitochondria.
- Minocycline – body fat.
- Excreted through glomerular filtration, except doxycycline.
- Secreted in milk- affect suckling infant.

ADVERSE EFFECTS:

- Irritative effect.
- Dose related toxicity
 - Liver damage
 - Kidney damage
 - Fanconi syndrome
 - Photo-toxicity
 - Effect on teeth and bone
 - Anti-anabolic effect
 - Increased intracranial pressure
 - Diabetes insipidus

- Vestibular toxicity
- Hypersensitivity
- Super infections

PRECAUTIONS:

- Avoided during pregnancy, lactation, & in children.
- Avoided in patients on diuretics
- Cautiously used in renal or hepatic insufficiency.
- Never use expired drugs.
- Avoid mixing injectable tetracycline with penicillin.

USES:

- Limited use in acute dental infections
- Broad spectrum of action, suppression of MMPases
- MMPases are calcium dependent, tetracyclines chelate calcium
- Scavenging free oxygen radicals
- GCF concentrations- 5 to 10 times greater than serum
- Binds to tooth surface and slowly released after stoppage
- Adjuvant role in chronic periodontitis refractory & juvenile periodontitis
- Refractory-2w{1g/day- tetracycline, dox-(0.1 to 0.2g/day) for gingival inflammations, normalise micro flora
- Active against actinobacillus species - > juvenile periodontitis

MINOCYCLINE:

- Broad spectrum of activity.
- Spirochetes & motile rods.
- Given twice daily.
- Less photo & renal toxicity than tetracycline.

- Reversible vertigo.
- 200mg/day for 1 week, reduces total microbial count.

DOXYCYCLINE:

- Same spectrum as minocycline.
- Given once daily.
- Absorption altered by calcium & other metal ions.
- Most photosensitizing.
- 100mg b.i.d on 1st day, followed by 100mg once daily is given, 50mg b.i.d to reduce GI upset.

CHEMICALLY MODIFIED TETRACYCLINES (CMT):

- Based on chemistry of tetracyclines, reviewed by Mitscher a number of tetracycline analogues are produced.
- Side chain deletion/ addition of moieties to parent molecule.
- Totally 10 modified forms are produced.
- CMT 1- 4-de-dimethylamino tetracycline.
- CMT 2- tetracyclinonitrile.
- CMT 3- 6-deoxy 6-demethyl 4-de-dimethylamino tetracycline.
- CMT 4- 7-chloro 4-de-dimethyl tetracycline.
- CMT 5- tetracycline pyrazole.
- CMT 6- 4-dedimethylamino 4-hydroxyl tetracycline.
- CMT 7- 12 α -deoxy,4-dedimethylamino tetracycline.
- CMT 8- 4-dedimethylamino doxycycline.
- CMT 9- 12 α ,14 α -anhydro,4-dedimethylamino tetracycline.
- CMT 10- 7-dedimethylamino 4-dedimethylamino tetracycline.

METRONIDAZOLE:

- Prototype drug of nitroimidazoles & introduced in 1959 for trichomonas vaginitis & later found to be anti-protozoal drug.
- Efficiency against anaerobes was a chance discovery & now used extensively to treat oral infections.
- Other members of nitroimidazole group are:
 - Tinidazole
 - Secnidazole
 - Ornidazole
 - Satranidazole

MECHANISM OF ACTION:

- Metronidazole enters the cell by diffusion
- Its nitro group is reduced to highly reactive nitro free radical.
- This nitro radical act as electron sink & competes with biological electron acceptor in anaerobes electrons generated in PFOR enzyme in pyruvate oxidation.
- Aerobic environment attenuates cytotoxicity of mitronodazole by inhibiting its reductive activation.
- Almost absorbed from small intestine.
- Widely distributed in body, attains therapeutic concentrations in saliva, CSF, vaginal secretions & semen.
- Metabolised in liver – oxidation & glucoronide conjugation.
- Excreted in urine
- Plasma $t_{1/2}$ – 8 hrs

ADVERSE EFFECTS:

- Anorexia, nausea, bitter or metallic taste & abdominal cramps – most common.
- Looseness of stools – occasional.
- Headache, glossitis, dryness of mouth, dizziness, rashes & transient neutropenia – less common.
- Prolonged use – peripheral neuropathy & CNS effects.

- Seizures – at very high doses.
- On i.v, thrombophlebitis of vein occurs if not diluted properly.

CONTRAINDICATIONS:

- Neurological disease
- Blood dyscrasias
- 1st trimester of pregnancy
- Chronic alcoholism

INTERACTIONS:

- Disulfiram like intolerance to alcohol.
- Enzyme inducers reduce the therapeutic effects.
- Cimetidine can reduce its metabolism.
- Enhances warfarin action by inhibiting its metabolism.
- It decreases renal elimination of lithium.

USES:

- To treat gingivitis, ANUG, periodontitis, aggressive periodontitis.
- Used as monotherapy/ combination with root planing & surgery/ with other antibiotics.
- Single dose 250mg orally appears in serum & GCF in sufficient amount.
- Systematically given to reduce growth of anaerobes, spirochetes, & decrease clinical & histopathological signs of periodontitis.
- Most common regimen- 250mg, t.i.d for 7 days.
- SODER et al showed that metronidazole was more efficient than placebo in management of sites unresponsive to root planing.
- Studies suggest that combination of amoxicillin or augmentin, metronidazole may have value in management of localised aggressive periodontitis/ refractory periodontitis.

CHLORAMPHENICOL:

- Initially obtained from streptomyces venezulae in 1947.
- Currently available products are all synthetic.

- Inhibit protein synthesis.
- High doses- inhibits mammalian mitochondrial protein synthesis.
- Bone marrow cells are specially susceptible.
- Primarily bacteriostatic, at high concentrations exerts cidal action.
- Rapid & complete absorption after ingestion.
- 50-60 % plasma protein bound.
- Primarily conjugated with glucuronic acid in liver & little is excreted unchanged in urine.
- Plasma $t_{1/2}$ - 3-5 hrs.
- Oral route is common- 250-500mg 6 hourly, children 25-50 mg/kg/day.

ADVERSE EFFECTS:

- Bone marrow depression.
- Hypersensitivity.
- Irritative effect.
- Super-infections.
- Gray baby syndrome.

USES:

- No indication to use in dentistry.
- Used in:
 - Enteric fever
 - Anaerobic infection
 - Intraocular infections
 - Topical- conjunctivitis, ear infections

AMINOGLYCOSIDES:

- Natural & semi-synthetic
- Polybasic amino groups linked glycosidically to 2 or more aminosugar residues.
- Streptomycin- 1st discovered in 1944 by Waksman & colleagues.
- All are synthesised by soil actinomycetes & have many common properties.

COMMON PROPERTIES OF AMINOGLYCOSIDES:

- All are sulfate salts, highly water soluble, solutions are stable for months.
- Ionize in solution, not absorbed orally, only extracellularly, do not penetrate brain or CSF.
- Excretion- unchanged in urine by glomerular filtration.
- Bactericidal & more active in alkaline medium.
- Act by interfering with bacterial protein synthesis.
- Active primarily against aerobes & do not inhibit anaerobes.
- Only partial cross resistance among them.
- Relatively low margin of safety.
- Show ototoxicity & nephrotoxicity.

CLASSIFICATION:

- | | |
|---------------|-----------|
| • Systemic: | topical: |
| -streptomycin | -neomycin |
| -gentamicin | -framycin |
| -kanamycin | |
| -tobramycin | |
| -amikacin | |

SHARED TOXICITIES:

- Ototoxicities
 - Cochlear damage

- Vestibular damage
- Nephrotoxicity
- Neuromuscular blockade

PRECAUTIONS & INTERACTIONS:

- Avoided in pregnancy: foetal ototoxicity.
- Avoid using with other ototoxic drugs, eg: high ceiling diuretics, minocycline.
- Avoid using with nephrotoxic drugs, eg: amphotericin B, vancomycin.
- Cautious use in middle aged & kidney damage patients.
- Caution in patients using muscle relaxants
- Do not mix with other drugs in same syringe.

USES:

- Streptomycin is not used in dentistry.
- Tuberculosis
- Subacute bacterial endocarditis
- Plague
- Tularaemia, etc
- Gentamicin 2mg/kg i.m/i.v (single dose) is used to supplement amoxicillin or vancomycin for prophylaxis.

MACROLIDES:

- They have macrocyclic lactone ring with attached sugars.
- Erythromycin is used from 1950's, later roxithromycin, clarithromycin, azithromycin are introduced.

ERYTHROMYCIN:

- Isolated from streptomyces erythreus in 1952
- Main alternative to penicillin.

- Frequently used in dentistry.
- Acid labile- enteric coated tablets.
- Incomplete absorption & food interference seen.
- Widely distributed in body.
- 70-80% is plasma protein bound.
- Partly metabolised & primarily excreted in bile unchanged
- Renal excretion is less.
- Plasma t_{1/2}- 1 1/2 hr, but persists longer in tissues.

ADVERSE EFFECTS:

- Erythromycin is a safe drug. But side effects do occur:
 - Gastrointestinal pain.
 - Reversible hearing impairment.
 - Hypersensitivity.

INTERACTIONS:

- It inhibits hepatic oxidation of many drugs leading to rise in plasma levels of:
 - Theophylline
 - Carbamazepine
 - Valproate
 - Warfarin
 - Terfenadine
 - Cisapride

USES:

- Given orally, safe, active against aerobic & anaerobic gram positive bacteria infecting orodental structures.
- 2nd choice drug to penicillin, less effective than penicillin.

CLINDAMYCIN:

- Lincosamide antibiotic similar mechanism & spectrum as erythromycin, it also exhibits partial cross resistance.
- Inhibits gram positive cocci, anaerobes, gram negative aerobes.
- Oral absorption is good.
- Accumulates in neutrophils & macrophages.
- Largely metabolised & are excreted in urine & bile.
- Plasma $t_{1/2}$ – 3hrs.

SIDE EFFECTS:

- Rashes, urticaria, abdominal pain.
- Major- diarrhoea & pseudomembranous enterocolitis due to C.difficile superinfection.
- Drug has to be stopped & metronidazole is given.

USES:

- A reserve drug – anaerobes where penicillin cannot be given/ macrolide / not responding with other.
- Good penetration into bones , so used for dentoalveolar abscess / bone infections.
- An alternative in prophylaxis.

VANCOMYCIN:

- Glycopeptide antibiotic-1956 as penicillin substitute.
- Inhibit bacterial cell wall synthesis.
- i.v
- $t_{1/2}$ – 6 hrs
- Excreted unchanged in glomerular filtration.

TOXICITY:

- Systemic toxicity is high.
- Conc. dependent nerve deafness(may be permanent)
- Kidney damage is dose dependent.

- Caution while giving oto & nephrotoxic drugs.
- Skin allergy & fall in B.P due to release of histamine .
- Red man syndrome.

USES:

- For cases not responding to others, hypertensive's.
- Vancomycin- 1g(20mg/kg) i.v infusion, an alternative to pencyllin allergics.

ANTIFUNGAL DRUGS:

- Drugs used for superficial & deep fungal infections.
- Use of anticancer/ immunosuppressant drugs, corticosteroids, broad spectrum antibiotics, dentures.
- Break down of host defence mechanism by above agents, saprophytic fungi invade host.

CLASSIFICATION:

- Antibiotics:
 - Polyenes
 - Heterocyclic benzofuran
- Anti metabolites:
- Azoles:
 - Imidazoles
 - triazoles
- Allylamine
- Others.

Used in dentistry:

- Amphotericin B
- Nystatin
- Clotrimazole
- miconazole

ANTI VIRAL DRUGS:

- Used to treat oropharyngeal lesions of:
 - Herpes simplex
 - Herpes labialis

CLASSIFICATION:

- Anti-herpes virus:
 - Idoxuridine, acyclovir, valacyclovir, etc
- Anti-retro virus:
 - NRTIs: zidovudine, lamivudine, stavudine.
 - NNRTIs: nevirapine, efavirenz.
 - Protease inhibitors: ritonavir, indinavir, nelfinavir
- Anti-influenza virus:
 - Amantadine, rimantadine, oseltamivir.
- Non-selective anti viral drugs:
 - Ribavirin, interferon α .

Most commonly used in dentistry are:

- Acyclovir
- valacyclovir

ANTIBIOTICS IN PERIODONTICS:

- Periodontal infections – bacterial deposits in supra & subgingival plaque.
- Infections respond well with reduction in bacterial load.
- With the evidence of bacterial specificity in periodontitis, use of antibiotics is increased over past 3 decades.

PERIODONTAL PATHOGENS:

- At least 500 bacterial taxa are identified within periodontal pocket.

PRACTICAL ASPECTS OF ANTIBIOTIC THERAPY:

- Conservative & selective approach
- Indiscriminate use is not recommended
- Agents targeting offending pathogen & bactericidal drugs are preferred.
- Empirical therapy is employed for diseases of known aetiology.
- Some studies support the use of microbial cultures, sensitivity testing in cases where no response is seen with conventional therapy.

RATIONALE & PRINCIPLES OF ANTIBIOTIC THERAPY:

- Major cause – bacterial biofilm.
- Mechanical therapy.
- Clinical studies – successful therapy for most of the periodontal diseases is by SRP & results can be maintained over long period only with patient's high level oral hygiene & regular professional maintenance.
- Studies say correlation between outcomes of therapy & microbes at the site of therapy is seen.
- Positive sites – further attachment loss.
- Mechanical therapy alone is not effective in all cases.
- Because some pathogens are at inaccessible sites.
- In addition, treated sites may be re-colonized.
- Complementing mechanical therapy with local or systemic antibiotics may enhance the effects & advantageous.
- Use of antibiotics has to be rational, because over years resistance may develop.
- Further may disturb the microbial flora / initiate new infection.
- All antibiotics may show inherent risk of toxicity.
- Hence, prescription of an antibiotic is a carefully weighed decision.
- An antibiotics have to fulfil the following:
 - Adequate concentration & length of time the antibiotic has to be maintained.
 - At these doses no major local & systemic adverse effects should occurs.
 - Data from previous studies should substantiate favourable outcomes.

- Finally, drug regimen should have a documented practical advantage over conventional therapy.

GUIDELINES:

- Clinical diagnosis & situation dictate the need of antibiotics.
- Disease activity may be indicative of periodontal intervention & microbial sampling.
- Antibiotics are selected based on patient's medical & dental status, current medications & results of microbial analysis, if performed.
- Samples are taken at beginning of an appointment before instrumentation of pocket. Supragingival plaque is removed & endodontic paper point is placed in a deepest pocket to absorb bacteria. It is transferred over night in reduced transfer fluids & the results are sent back with appropriate antibiotic regimen.
- Meta-analysis of randomised clinical trials & quasi studies show – systemic antibiotics improve attachment levels as an adjunct. Same results cannot be obtained with stand alone therapy with antibiotics.
- An antibiotic as adjunct in SRP improves attachment levels in chronic & aggressive periodontitis, although aggressive periodontitis have experienced greater benefits.
- Identification of an effective antibiotic against periodontal disease was limited due to insufficient sample size in randomised clinical trials of a systemic review. Using meta-analysis 8 different antibiotics were evaluated, only tetracycline & metronidazole have shown to improve the condition along with SRP.
- Debridement of root surfaces, optimal oral hygiene, and frequent periodontal maintenance therapy are important for comprehensive periodontal therapy. Antibiotic strength of 500 times greater than systemic therapeutic dose is needed to destroy bacteria arranged in biofilm. So it is important to mechanically disrupt biofilm so that antibiotics can be effective.
- Although adequate data suggesting the use of systemic antibiotics benefit in treating destructive periodontitis, limited data is present suggesting what type of antibiotic to be used for particular infection, optimum dosage, frequency & duration of therapy & long term outcomes of the therapy, potential hazards & economic ramifications.
- There is no best choice of antibiotic at present (no silver bullet) . Therefore integration of h/o patient disease, clinical signs & symptoms, radiographic & microbial examination determine the course of antibiotic therapy.
- The clinician must make the final decision with the patient. Risks & benefits concerning antibiotics as adjunct to the therapy should be discussed with the patient before their use.

DRUG DELIVERY ROUTES:

- Two routes :
 1. Systemic route.
 2. Local route.
- Each mode has its potential advantages & disadvantages.

COMPARISON OF LOCAL & SYSTEMIC ROUTES:

Issue	Systemic route	Local route
Distribution	Wide	Narrow
Concentration	Variable levels in different regions of the body	High dose at local site, low at other sites
Therapeutic potential	Reaches widely distributed microbes better	Act locally on biofilm associated bacteria
Problems	Systemic side effects	Re-infection from non-treated sites
Limitations	Good patients compliance	Infection should be limited to treated site
Diagnosis	Identify pathogen Choice of drug	Distribution pattern of lesion & pathogen, treated

SYSTEMIC ANTIBIOTIC THERAPY:

- Advantages:
 - Wide distribution so that all distribution sites get treated.
 - So, both oral & extra dental sites are treated.
- Disadvantages:
 - Less GCF concentration
 - Systemic toxicity may occur
 - Organisms may develop resistance
 - Patient compliance.

COMBINATION THERAPY:

- **No single pathogen is effective against all putative pathogens.**
- **Mixed infections require more than one antibiotic, either serially or in combination.**
- **Rams & Slots reviewed combination therapy with systemic metronidazole along with amoxicillin, amoxiclavulanate or ciprofloxacin.**
- **Metronidazole – amoxicillin & metronidazole – augmentin combinations provided excellent elimination of organisms in adult periodontitis & LAP, that had been treated unsuccessfully with tetracyclines & mechanical debridement.**
- **Ticono et al found metronidazole & amoxicillin to be clinically effective for LAP, although 50% harboured A.a one year later.**
- **Metronidazole – ciprofloxacin is effective against A.a, metronidazole acts on obligate anaerobes, whereas ciprofloxacin on facultative anaerobes.**

LOCAL DRUG DELIVERY:

- **Goodson et al in 1979 1st proposed the concept of controlled drug delivery in treating periodontitis.**
- **1st device – hallow fibers of cellulose acetate filled with tetracycline.**
- **To complement non-surgical therapy, there are multiple antibiotics that can be given locally into mucosa like metronidazole, chlorhexidine, minocycline, doxycycline, tetracycline.**

- These drugs are used in periodontal pockets & can inhibit or eliminate periodontal pathogens as well as modulate inflammatory response of tissue.

- Greenstein & Tonetii, 2000.

CRITERIA:

- Drug must reach the target site.
 - And it should be at effective concentration in the target site.
 - And should last for an adequate period of time.
- Goodson(1989) & Greenstein & Tonetii (2000).

RATIONALE & PRINCIPLE OF LDD PERIODONTICS:

- The principle behind LDD that GCF contained within the pocket serves as a leaching medium for drug discharge from the solid form & for its disposal in the pocket & as a regular spot for treating.
- The rationale of LDD is to remove any residual infective/ inflammatory elements still harbouring in periodontium that are not reachable to mechanical debridement.
- Most important goal is the prolonged obtainability of drug in sufficient minimum inhibitory concentrations over a required period of time.

CLASSIFICATION:

- Based on the application:
 - Personally applied.
 - Professionally applied.
- Based on duration of medicament:
- Sustained release – for less than 24 hrs.
- Controlled release – atleast 1-3 days.
- Based on degradability:
 - Non – biodegradable devices.
 - Degradable devices.

INDICATIONS:

- Sites where inaccessible for SRP in deep pocket.
- In refractory periodontitis.
- Sites not responding following repeated SRP in localised pockets.
- As an alternative to antibiotics in acute periodontal abscess.

CONTRAINDICATIONS:

- Pregnant & lactating patients if drugs show harmful effect.
- Aggressive forms where systemic antibiotics are more effective.
- In patients allergic to the components of LDD.

TETRACYCLINE:

- 1st available.
- Made of ethylene/ vinyl acetate copolymer fiber of D=0.5 mm, with 12.7mg/9 inches of tetracycline.
- It is marketed under the name Actisite & is approved by FDA.
- Safe, inert & non-resorbable copolymer with 25% w/w tetracycline HCL.
- Remains persistent in concentration >1000µg/ml for 10 days.
- Periodontal plus AB- recent bioresorbable (7 days) tetracycline fibers & require single appointment.
- Newman et al has done a study on adjunctive tetracycline fiber therapy, they showed marked success of SRP in treating localised recurrent periodontitis in SPT.

DOXYCYCLINE:

- ATRIDOX: FDA approved 10% doxycycline in gel form reaching upto 1500-2000 µ/ml in 2 hrs.
- Supplied as 2 syringes:
- One with 42.5mg doxycycline.
- Another 450 mg ATRI gel delivery system, a flowable polymer (mix of 36.7% poly-DL-lactide dissolved in 63.3% N-methyl-2-pyrrolidone)

- The fillings of 2 syringes are mixed & locally applied by placing in periodontal pocket, that flows to bottom of the pocket, fills the gap between the tooth & gums.
- Gel hardens on contact with saliva to wax like consistency & slowly released for 21 days.
- *P.gingivalis*, *F.nucleatum* are also susceptible to doxycycline at concentration of 6µg/L as per some studies.

SUBGINGIVAL MINOCYCLINE:

- Films, microspheres & ointment forms.
- Film: ethyl cellulose film contains 30% of minocycline, cause complete elimination of pathogen in 14 days.
- Microspheres: ARESTIN an FDA approved sustained release form of 2% minocycline microspheres.
- Each syringe contain 4mg microspheres =1mg minocycline.
- Once introduced subgingivally, they adheres to walls of pocket, polymer is hydrolysed by GCF & water filled channels are formed in microspheres providing encapsulated drug to be released.
- Minocycline diffuses over 2 weeks & end result is 340µ/ml attained in pocket.
- Advantage is ease of applying & disadvantage is single use product.
- Ointment: dentomycin, periocline – 2% minocycline gel reaching 1300µ/ml in 1 hr & reduced to 9µ/ml after 7hrs.

METRONIDAZOLE:

- Monotherapy & combinations.
- Gingivitis, ANUG, chronic periodontitis, aggressive periodontitis.
- ELYZOL:
- Oil based gel form – 25%.
- After applying gel acquire flow & fills pocket.
- Highly effective for atleast 8 hrs at concentration >100µl/ml & 1µl/ml after 36 hrs.
- Gel is applied twice a week for 14 days, dosage depends on number of the teeth.
- For 6-8 teeth, 0.3 g gel is used.

SUBGINGIVAL CHLORHEXIDINE:

- **Commonly used mouth rinse.**
- **Reduces pellicle formation, alters attachment of bacteria to the tooth.**
- **Exhibits high substantivity being cationic in nature.**
- **Mouth rinses, gels, varnishes, chip.**
- **Positively charged CHX bind to cell surface -> disrupts & enter cell -> disrupt cytoplasm & drifts out of cell -> death**

Periochip:

- 1st launched in US dental market in 1998.
- Wt – 7.4 mg, stored at 20-28 degrees.
- Later room temperature chips are introduced with longer shelf life (2yrs).
- Orange brown coloured biodegradable, rectangular chip – 2.5 mg of CHX released in biphasic manner initially x- 40 % in 24 hrs.
- Remaining in 7-10 days span.
- Polymer is made of 3.4 mg cross-linked hydrolysed gelatin, 0.5 mg gelatin, 0.96 mg purified water, 2.5mg CHX.
- After placing in pocket, its antiseptic property kills microbes slowly.

Periocol-C- a orange brown rectangular.

- One end rounded for insertion into pocket.
- Prepared by incorporating 2.5mg CHX from 20% solution in type1 biodegradable collagen membrane from fish.
- In 24 hrs – 40-45% CHX is released,
- Rectilinear mode for 7-8 days.
- Described as initial burst effect due to diffusion of CHX from LDD system, followed by release due to enzymatic degradation.
- Chlosite : 1.5 % CHX gel, xanthan based preparation.
- Other LDD systems:

- Clarithromycin gel – subgingival delivery-0.5%
- Herbal products : aloe vera, neem, tulsi, propolis, cocoa husk, pomegranate, cranberry.
- Colloidal drug carriers: micelles, emulsions, liposomes, nano-particulates.
- PT-01 – subgingival delivery of ofloxacin.

ADVANTAGES OF LDD:

- Maintain optimal concentrations for prolonged time, without side effects.
- Patient compliance better than systemic antibiotic therapy.
- subgingival antibiotic levels is 100 times greater than systemic therapy.
- Antibiotic resistance & super infections are not seen.
- As part of home self care LDD can be applied by patient.

DISADVANTAGES:

- Time consuming & labour.
- In areas adjacent to tongue, tonsils, buccal mucosa LDD may not be effective due to reinfection.
- Inaccessible areas cannot be dealt.

FAILURES OF ANTIBIOTIC THERAPY:

- Improper selection of drug, dose, route, duration of treatment.
- Treatment started too late.
- Adjunct measures are not taken.
- Poor host defence.
- Ineffective organisms as barriers.

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