**Pharmacology 11 year 2020 clinical med class**

**Outcomes**

1. Demonstrate understanding of antibacterial drugs and their uses
2. Treat fungal infections using the various antifungal drugs
3. Prescribe antiviral agents appropriately
4. Demonstrate understanding of the various topical agents and antiseptics, and their uses.

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| **Week 1:** |  |  | **Antibacterial Agents;**introduction to antimicrobials – classification of antimicrobials, mechanisms of action of antimicrobials, principles of antimicrobial treatment, problems associated with antimicrobial use, rational use of antimicrobials. |

**Classification of antimicrobials**

* antibiotics/antibacterials
* antifungals
* antivirals
* antihelminthics
* antiparasitics

**Antibacterial/ antibiotics classification according to chemical structure.**

1. Beta lactams. a) penicillins, carbapenems, monobactams, cephalosporins
2. aminoglycosides e. g gentamycin, streptomycin, neomycin, tobramycin, amikacin,spectinomycin
3. tetracyclines e. g

Chlortetracycline hydrochloride Oral, IV

Oxytetracycline hydrochloride Oral, IV

Demeclocycline hydrochloride Oral

Methacycline hydrochloride Oral

Doxycycline Oral,

Minocycline hydrochloride Oral, IV

1. macrolides e.g erythromycin, azithromycin
2. chloramycetins and chloramphenicol
3. lincosamides e.g clindamycin and lincomycin
4. sulfonamides e.g cotrimoxazole
5. nitrofurans e.g nitrofurantoin
6. quinolones 1,2,3,4th generation classification

1st generation- **nalidixic acid** and **cinoxaci**n;

2nd generation -n**orfloxacin**, **ciprofloxacin**, **ofloxacin**, **enoxacin**, and **lomefloxacin**

3rd generation--**levofloxacin**, **sparfloxacin**, **gatifloxacin**;

4th generation - **trovafloxacin** and **moxifloxacin**.

1. Bacitracin and the polymyxins are polypeptide e.g vancomycin
2. nitroimidazoles e.g metronidazole
3. anti tb ; 1st line and 2nd line
4. anti leprosy

**beta lactams.**

1. **penicillins,**

**Narrow spectrum**

i) Natural Penicillins

ii) Antistaphylococcal (penicillinaseresistant) Penicillins

* Natural penicillins

Penicillin G

Penicillin V

Benzathine P Procaine P

* Penicillinase R Methicillin (Spectrum of activity S. aureus, S. Epidermidi)

Nafcillin IM, IV

Oxacillin IM, IV

Cloxacillin Oral

Dicloxacillin

**Broad spectrum penicillins**

* **aminopenicillis**

Amoxycillin

ampicillin

* **Aminopenicillin/ B lactamase Inhibitors**

Sulbactam and clavulanate

inactivate the B lactamases and broaden aminopenicillin activity:

Some S. Aureus, many enterobacteriaceae, clostridia except difficile, Bacteroides spp

* **antipseudomonal penicillin/Extended spectrum**

Carbenicillin Oral

Mezlocillin IM, IV

Piperacillin IM, IV

Ticarcillin IM, IV

1. **carbapenems e.g broad spectrum(G+ve and –ves, anaerobes Resistant to B lactamases**

Imipenem

Meropenem

Ertapenem

1. **monobactams** e.g **A**ztreonam good for G –ve
2. **cephalosporins ; 1,2,3,4,5th generation**

**1st gen** 🡪**Spectrum of activity good cover for aerobic G+ve cocci(staph/strep) & some g -ve**

Cefadroxil

Cephalexin

Cephradine

Cefazolin IM, I

**2nd gen** 🡪**Spectrum of activity against, aerobic G-ve and facultative(E.coli,P.mirabilis,H.infl, b fragilis.**

Cefaclor PO

Cefamandole

Cefuroxime PO

Cefoxitin IM,IV

**3rd gen** 🡪**Spectrum of activity above +B burgdorferi, greater activity against aerobic G-ve than 2nd gen, shortlived activity againstenterobacteriaceae, no activity against p.aeroginosa except ceftazidime**

Cefixime

Cefotaxime

Ceftazidime

ceftriaxone IV,IM

**4th gen** 🡪**spectrum of activity antipseudomonal and antistaph cover, also enterobacteriaceae**

Cefepime

**5th gen**

Cefaroline

ceftoprole

**Classification of antibacterial agents according to mechanism of action**

Inhibition of cell wall synthesis; Penicillins, Cephalosporins, Monobactams ,Vancomycin

Inhibition of DNA gyrase ; Quinolones

Inhibition of RNA polymerase ; Rifampicin

Inhibition of protein synthesis; Aminoglycosides, Tetracyclines, Erythromycin, Chloramphenicol

Inhibition of folic acid metabolism/antimetabolites; Trimethoprim, Sulphonamides

**Classification of antibacterial agents into bactericidal and bacteriostatic**

**Bactericidal-** kill susceptible bacteria; e.g Penicillins, Cephalosporins, Aminoglycosides, Co-trimoxazole. **Bacteriostatic-** inhibit growth of bacteria; e.g; Erythromycin, Tetracyclines, Chloramphenicol, Sulphonamides, Trimethoprim.

**Mechanism of action of antimicrobial/ Antibiotics (2hrs)**

Antibiotics act by disrupting various molecular targets within bacteria and cell surface, preventing growth or initiating killing. (Bactericidal or bacteriostatic)

3 broad mechanisms:

• Disrupt bacterial cell envelope

• Block production of new proteins

• Inhibit DNA replication

**MOA can be summarized basing on site of action as;-**

* on the cell wall- interfere with the function of the cell by allowing it absorb water and burst, e.g penicillins, cephalosporins, vancomycin,bacitracin and cycloserine.
* Protein synthesis interference in bacteria ribosomes.e.g chloramphenicol, tetracyclines, erythromycin, aminoglycosides and fusidic acid.
* Antimetabolites; interferes with folic acid synthesis.
* Nucleic acid metabolism by interfering with DNA synthesis directly e.g quinolones and rifampicin on RNA or indirectly e.g sulfonamides and trimethoprim.
* Cytoplasmic membrane, e.g polymixins, polyenes like nystatin and amphotericin b

**Site of action for antibiotics**



 **General principles of antimicrobial therapy for good practice (2hr)**

1. make proper diagnosis including collecting samples for laboratory investigations before treatment
2. remove barriers to treatment e.g drain the abscess before antibiotics
3. decide whether therapy is really necessary e.g acute infections needs urgent therapy
4. Select the best drug depending on; drug specificity, pharmacodynamics, pharmacokinetics and patient previous history or allergy, less toxic drug and less cost to pt. The choice of antibacterial drug, together with its dose and route of administration, depend on the infection (in particular the responsible pathogen(s), but also anatomical site and severity), absorption characteristics of the drug, and patient factors (in particular age, weight, renal function liver function, pregnancy and lactation, allergy, immune status).
5. Administer the drug in optimum dose and frequency and correct route. Influenced by the severity of the disease, age, wt and std guidelines per country.
6. Continue therapy until cure has been achieved e.g 5 days for simple and >14 days for complicated infections like typhoid meningitis, tuberculosis. The duration of therapy depends on the nature of the infection and response to treatment.
7. encourage compliance to therapy by use of less frequency drugs
8. Test for cure by clinical monitoring and laboratory tests also some drugs require routine plasma concentration monitoring (e.g. aminoglycosides, vancomycin).
9. Prophylactic chemotherapy for surgical, bacterial endocarditis and dental procedures limited e. g start at the time of surgery and continue for 48hrs. If long duration change to oral antibiotics. Choose a narrow spectrum and possibly bactericidal antibiotic.
10. For most bacterial infections other than those involving bone, joint or heart valve tissue, five to seven days of treatment are sufficient.

Prophylaxis should be restricted to cases where the procedure commonly leads to infection.

The antimicrobial preferably be bactericidal and directed against the likely pathogen.

The aim is to provide high plasma and tissue concentrations of an appropriate drug at the time of bacterial contamination. Im inje. can be given with premedication or iv at the time of induction.

**Importance of combining antimicrobials**

* 1. For potentiation, synergism (e.g. use of co-trimoxazole in the treatment of Pneumocystis carinii pneumonia).
	2. delay development of drug resistance like for chronic disease management (e.g.TB)
	3. fixed dose combinations to enhance adherence and prevent resistance
	4. broaden spectrum of antibacterial activity in known mixed infections where lab is not possible or in bowel perforation, to achieve broad antimicrobial activity in critically ill
	5. Patients with an undefined infection (e.g. aminoglycoside plus penicillin to treat septicaemia).

**Problems associated with antimicrobial drugs (2hrs)**

**Resistance:** What the pathogen does to the drug. E. g some strains of Pseudomonas aeruginosa produce a plasmid-mediated adenylase that inactivates gentamicin by chemically altering its structure.

* + Resistance to drugs. Due to resistant strains, spontaneous mutation of resistant strains, transmission of resistant strains amongst host. Can be avoided by using fixed dose combinations, prescribing for correct indication and duration, monitoring resistance patterns in hospital or community, correct laboratory and clinical judgment.
	+ Opportunistic infection arising in immune compromised patients e.g by candida albicans, e coli, clostridium difficile. treat with iv combined bactericidal drugs
	+ Antibiotic associated(amoxil, ampicillin, cephalosporins,lincomycins) colitis/pseudomebrenous colitis by altering the gut normal flora. presents with diarrhea, mucoid or bloody, abdominal pain,leucocytosis and dehydration.3 wks hx of drugs. stool microscopy clostridium difficile. mx vancomycin 125mg qid for 5days.
	+ masking infections
	+ treatment failure which may be caused by; Drug resistance natural or acquired, late initiation of therapy, organism isolated not being the cause of disease, suboptimal use, barriers to access the target sites and reduced host defense system by diseases like HIV, leukemia and anticancer drugs.

**Mechanisms of drug resistance can be broadly divided into three groups:**

* Restriction of entry of the drug into the bacterium by altered permeability or efflux pump (e.g. sulphonamides, tetracycline);
* inactivation of the antimicrobial agent either by disruption of its chemical structure (e.g. penicillinase) or by addition of a modifying group that inactivates the drug (e.g. chloramphenicol is inactivated by acetylation);
* The b-lactam resistance of Streptococcus pneumonia is due to the appearance of altered penicillin binding proteins.
* Modification of the bacterial target – this may take the form of an enzyme with reduced affinity for an inhibitor, or an altered organelle with reduced drug-binding properties (e.g. erythromycin and bacterial ribosomes).

**How to limit resistance to drugs**

Avoid prescribing antibiotics to treat flue or no pneumonia patients

Take good history to determine if there is indication and duration of treatment

Monitor resistance patterns in hospital and community

Use combination therapy for TB, LEPROSY

Restrict drug use basing on the lab results, drug specifity.

**RATIONALE ANTIBIOTIC USE (2hrs)**

*Rationale drug use requires that patients receive medicines appropriate to their clinical needs, in doses that meet individual requirements, for an adequate time, at lowest cost to them and the community (WHO 1985)*

**Irrationale antibiotic use by prescribers and the patient.**

* irrational prescribing at work place due to lack of lab, workload, education
* use of antibiotics unnecessary e.g for common cold and diarrheoa
* wrong drug for specific condition
* overprescribing or multiple prescribing
* drugs with un proven efficacy or unsafely drugs( irrational dug policy)
* incorrect administration of drugs, incorrect dosing, and duration of treatment
* use of unnecessary expensive drugs
* failure to provide safe and effective drugs( supply chain system /procurement)
* patient taking antibiotic without a prescription
* skipping doses, irregular intervals
* saving or sharing antibiotics

**Irrationale consequeces**

* Increased drug resistance due to increased resistant strains of bacteria.
* increased morbidity and mortality due to reduced quality of drug therapy
* waste of resources e.g. vital drugs and increased cost
* increased unwanted ADR
* Increased treatment failures
* increased demand for drugs or pills for every illness

**What to consider when making a rational choice of antibiotic**

1. Therapeutic considerations; infective organism lab investigation e.g staph aureaus. disease severity, coexisting disease, avoid ADR, drug interaction
2. The pk absoption ; if vomiting give iv, distribution to tissue/site e.g ampiciclox 🡺tissues ,metabolism liver dse, excretion avoid aminoglycosides in renal failure
3. The p-dynamics-drug interaction What the drug does to the patient.For example, erythromycin stimulates gut motilin receptors and may induce nausea, patient may stop taking
4. Patients compliance; good for once, or bd antibiotics
5. Cost of the drug e.g less expensive is affordable to patients
6. **Cell wall synthesis inhibitors: β lactam antibiotics/** **Penicillins, Cephalosporins, Monobactams, Vancomycin**

Penicillins have a bactericidal action.

The bacterial cell wall synthesis is a cross-linking of adjacent peptidoglycan (murein) strands by a transpeptidation reaction, where by bacterial transpeptidases /PBP cleave the terminal D-alanine from a pentapeptide on one peptidoglycan strand and then cross-link it with the pentapeptide of another peptidoglycan strand. These 🡺 structural integrity to bacterial cell walls and permit bacteria to survive environments that do not match the organism’s internal osmotic pressure.

• The BETA-lactam contain β lactam ring which mimics the D-alanyl- D alanine portion of the peptide chain that is normally bound by **p**enicillin-**b**inding **p**roteins/**D-D transpeptidases** (PBPs) that assemble the peptidoglycan layer of bacterial cell wall. PBPs are involved with assembly, maintenance, or regulation of peptidoglycan cell wall synthesis. When beta-lactam antibiotics inactivate PBPs by binding irreversibly to PBP active site🡺 weakened bacteria cell wall/ lysis of bacteria inhibiting cell all synthesis.. The intact beta-lactam ring is required for antibiotic action.

**NB**/Penicillins have a bactericidal action. They inhibit cell wall synthesis by preventing the formation of peptidoglycan cross-bridges in actively multiplying bacteria.

**Mechanisms of resistance bacteria resistance**

A number of microorganisms have evolved mechanisms to overcome the inhibitory actions of the beta-lactam antibiotics. Bacteria develops resistance by synthesizing a beta lactamase enzyme which breaks the b lactam ring🡺 resistance.

There are **fou**r major mechanisms of resistance: Inactivation of the beta-lactam ring by beta lactamase enzyme

1. Alteration of Penicillin Binding Proteins( pbps)
2. reduction of antibiotic access to PBPs
3. Elaboration of antibiotic efflux mechanisms.

The most important mechanism of resistance is hydrolysis of the β-alactam ring by beta-lactamases ***(penicillinases and cephalosporinases).*** Many bacteria ***(Staphylococcus aureus, Moraxella [Branhamella] catarrhalis, Neisseria gonorrhoeae, Enterobacteriaceae, Haemophilus influenzae, and Bacteroides spp.)*** possess beta-lactamases that hydrolyze penicillins and cephalosporins.

**Cell wall synthesis inhibitors: GLYCOPEPTIDES: vancomycin and teicoplanin**

* Bacteriostatic. Bactericidal in vitro.
* The glycopeptides are inhibitors of cell wall synthesis.
* They bind to the terminal carboxyl group on the Dalanyl- D-alanine terminus of the N-acetylglucosamine- N-acetylmuramic acid peptide and prevent polymerization of the peptidoglycan layer by peptidoglycan synthase. (preventing the pbps from adding them to the pepidoglycan layer like the beta lactams)
* Gram-positive rods, such as Bacillus anthracis, Corynebacterium diphtheriae, Clostridium tetani, and Clostridium perfringens.
* They are not effective against gram-negative rods, mycobacteria or fungi.
* Effective against nearly all aerobic and anaerobic G+ves including C. difficile.

**Lipoglycopeptide: telavancin**

* New antibiotic for vancomycin R organisms
* Dual mechanism of action: cell wall synthesis inhibiton
* Binds to the terminal acyl-d-alanyl-d-alanine chains preventing cross-linking; disrupts cell membrane as well.

**Bacitracin**

Is a mixture of polypeptide antibiotics produced by Bacillus subtilis.

Prevents cell wall synthesis by binding to a lipid pyrophosphate carrier that transports cell wall precursors to the growing cell wall. As with penicillin, it contains a thiazolidine nucleus attached through L-leucine to a peptide composed of both D- and L-amino acids.but does not contain a beta-lactam ring.

1. **Mechanisms of protein synthesis inhibitors e.g aminoglycosides,** **Tetracyclines .Erythromycin. Chloramphenicol**

• Interact with various components of the bacterial ribosome and inhibit its function

**Aminoglycosides**

* They are **bactericidal**
* Have a Positive charge allowing them bind to the negatively charged outer bacterial membrane with formation of transient holes through which antibiotic molecules move🡺disruption of membrane integrity.
* Also penetrate the inner cytoplasmic membrane and bind the 30S subunit of the bacterial ribosome inhibiting synthesis of new proteins from mRNA to peptides.
* They have post antibiotic effect characterized by prolonged suppression of bacterial regrowth. this explains why aminoglycosides can be given in single daily doses despite their short half-lif
* Good activity against aerobic G-ves bacilli, like Escherichia coli and Klebsiella pneumoniae, and Proteus, Serratia, Acinetobacter, Citrobacter, and Enterobacter spp. Gentamicin also has significant activity against Staphylococcus aureus. No activity on anaerobes.
* Used synagistically with beta lactams empirically for sepsis.

**Macrolides e.g erythromycin**

* B**acteriostat**ic
* Bind tightly to the 50 s ribosomes subunit preventing exit of newly synthesized peptide and hence blocking protein production.
* Macrolides bind to the 50S ribosomal subunit of bacteria but not to the 80S mammalian ribosome; this accounts for its selective toxicity. Binding to the ribosome occurs at a site near peptidyltransferase🡺inhibition of translocation, peptide bond formation, and release of oligopeptidyl tRNA.
* Active against a broad variety of bacteria: some G+ves, G-ves, atypicals, some mycobacteria and spirochaetes

**Tetracyclines and Glycylcyclines**

* Bacteriostatic
* Interact with the 30s subunit of the bacterial ribosome and prevent binding by **(tRNA) (transfer** ribobnuceic acid) molecules blocking protein synthesis. n.b; tRnA is a molecule that decodes the mRNA into a bacterial protein in the ribosomes during translation.
* Active against some aerobic G+ves, some aerobic G-ve, including Rickettsia, Coxiella, Mycoplasma, and
* Chlamydia spp.. atypicals and spirochaetes

**Chloramphenicol**

* Bacteriostatic
* Chloramphenicol is a nitrobenzene derivative that affects protein synthesis by binding to the 50S ribosomal subunit and preventing peptide bond formation (blocking the binding of tRNA loaded with an amino acid).
* Less limited use in resource rich due to toxicity concerns-reversible dose dependent BM suppression
* Broad spectrum: aerobic G+ves, aerobic G-ves, anaerobes and atypicals
* A broad-spectrum antibiotic that is effective against gram-positive and gram-negative bacteria, including Rickettsia, Mycoplasma, and Chlamydia spp. and anaerobic bacteria, including Bacteroides fragilis.

**Clindamycin and Lincosamide antibiotic**

* bactericidal
* bind to the 50s subunit of the bacterial ribosome
* They bind to the 50S ribosomal subunit at a binding site close to or overlapping the binding sites for chloramphenicol and erythromycin. blocks peptide bond formation by interference at either the A or P site on the ribosome and inhibit bacterial protein synthesis
* Active against aerobic G+ves and anaerobes. staphylococci and streptococci other enterococci. Also, against S. pyogenes (group A strep) and Corynebacterium acnes
* No activity on aerobic G-ves
* Associated with C. Difficile/pseudomembranous colitis in man.

**Linezolids e.g** oxazolidinones

* bind to the 50s subunit of the ribosome preventing association with the 30s subunit
* also inhibits protein syntheis by preventing formation of the first peptide bond
* Activity against aerobic G+ve including MRSA,VRE but not approved for penicillin R stre
1. **Antimetabolites: Sulfa d*r*ugs ;**Trimethoprim-sulfamethoxazole and dapsone
* They are bacteriostatic drugs.
* Inhibitors of folic acid synthesis (bacteria cannot use preformed folic acid).
* The sulfonamides reversibly block the synthesis of folic acid. Humans cannot synthesize folic acid and must acquire it in the diet; thus, the sulfonamides selectively inhibit microbial growth.
* Sulfonamides and sulphones are ***p****-***a**mino**b**enzoic **a**cid (PABA) analogues, competitive inhibition of dihydropteric acid, which is necessary for PABA to be incorporated into dihydropteroic acid, an intermediate compound in the formation of folinic acid.

*Folic. A. functions as a coenzyme in transfer of 1-carbon units required for synthesis of thymidine, purines, and some amino acids.* ***F. acid*** *consists of 3 components: a pteridine moiety, PABA, and glutamate.*

* trimetoprim inhibits bacterial growth by preventing the synthesis of tetrahydrofolate.
* Broad variety of aerobic G+ve and G-ve susceptible like the Enterobacteriaceae, active against E. coli, moderate activity against Proteus mirabilis and Enterobacter spp. Chlamydia spp.
* Sulfonamides are active on parasitic infections. e.g Toxoplasma gondii and occasionally chloroquine- resistant Plasmodium falciparum.
* No activity on atypicals and anaerobes and pseudomonas
* Sulfacetamide and sulfadiazine [silver salt]) are designed for topical use such as in infection of the eye and in burn patients.
1. **Inhibitos of DNA synthesis: Quinolones**
* The effect of quinolones on the DNA enzymes is initially **bacteriostatic** but becomes **bactericidal** when bacteria are unable to repair the DNA lesions.
* All except nalidixic acid have fluorine added to enhance potency
* They contain a carboxylic acid moiety in the 3-position of the basic ring structure (the 4-quinolones).
* Quinolones inhibit DNA synthesis through their specific action on DNA gyrases, which are composed of two A and two B subunits. DNA subunits A (gyrase A gene) have a strand-cutting function to prevent overwinding (supercoiling) of the DNA strands during separation and eventual replication of the mirror strand. The A subunits are the site of action for the 4-quinolones.
* Binds to the A sub-unit of DNA gyrase, prevent supercoiling of DNA.
* Broad variety: G+ve, G-ve, atypicals and mycobacteria
1. **Inhibitors of RNA synthesis: Rifamycins e.g rifampicin**
* Inhibit bacterial RNA polymerase
* Activity against staph, N. Meningitidis and H. Influenza
* Used in combination treatment for mycobacterial infections

**Metronidazole**

* Small molecule that can passively diffuse into bacteria.
* Has a nitro group that must be reduced (accept electrons) for it to be active.
* Anaerobic bacteria can donate electrons to this nitro group enabling it to form free radicals that lead to breaks in DNA molecules and subsequent cell death
* Active against G+ve and –ve anaerobes including C. Difficile and microaerophilic H. pylori

**Lipopeptides** e.g **Daptomycin**

* has a lipid portion that inserts into the bacterial cytoplasmc membrane forming an ion conducting channel that allows ions to escape from the bacterium🡺cell death
* Active against aerobic G+ves, penicillin R S.pneumo, some VRE
* No activity against G-ves, poor activity in lungs

**The polymyxins**

They are polypeptide antibiotics that contain both hydrophilic and lipophilic regions.

They accumulate in the cell membrane and probably interact with membrane phospholipids.

The fatty acid portion of the antibiotic penetrates the hydrophobic portion of the membrane phospholipid and the polypeptide ring binds to the exposed phosphate groups of the membrane🡺distortion of the membrane, impair its selective permeability, produce leakage of metabolites, and inhibit cellular processes.

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| **Week 2:** |  |  | **Antibacterial Agents;**Drugs that inhibit cell wall synthesis: beta lactam antimicrobials – penicillins |

**BETA LACTAMS (2hr) ; inhibits bacterial cell wall synthesis**

1. **PENICILLINS**

The penicillin is a large group of bactericidal compounds.

They can be subdivided and classified by their chemical structure and spectrum of activity (broad or narrow). The structure common to all penicillin’s is **a beta-lactam ring fused** with a thiazolidine nucleus. The antimicrobial activity of penicillin resides in the β-lactam ring. Splitting of the β-lactam ring by either acid hydrolysisor β-lactamases results in the formation of penicilloic acid, a product without antibiotic activity🡪 resistance. The most important mechanism of resistance is hydrolysis of the β-lactam ring by **β-lactamases** (penicillinases and cephalosporinases). Many bacteria (*Staphylococcus* *aureus, Moraxella* [*Branhamella*] *catarrhalis,* *Neisseria gonorrhoeae,* Enterobacteriaceae, *Haemophilus* *influenzae,* and *Bacteroides* spp.) possess β-lactamases that hydrolyze penicillins and cephalosporins.

**MOA;** inhibits bacterial cell wall synthesis

Blocking a critical step in bacterial cell wall synthesis.

Bacterial transpeptidases covalently bind the β-lactam antibiotics at the enzyme active site, and the resultant acyl enzyme molecule which is stable and inactive.The intact B-lactam ring is required for antibiotic action.

The B-lactam ring modifies the active serine site on transpeptidases and blocks further enzyme function. β-lactam antibiotics inactivate penicillin binding proteins (PBPs)🡺 structurally weakened cell wall of bacterium🡪 cell lysis and death.

**classification**

**Narrow spectrum**

a) Natural Penicillins

b) Antistaphylococcal (penicillinase resistant) Penicillins

**a) Natural Penicillins**

**1) Penicillin G (benzylpenicillin) xpen i.v or i.m**

It’s the drug of choice for streptococcal, pneumococcal, gonococcal and meningococcal infections, and is also useful for treatment of anthrax, diphtheria, gas gangrene, leptospirosis, syphilis, tetanus, yaws

**PK**

It is an acid-labile compound with variable bioavailability after oral administration thus not orally used.

It distributes to most tissues and serosa-lined cavities, although low concentrations appear in breast milk and CSF.

In inflamed meninges the concentrations in CSF approx. 5% of the serum concentration.

In inflamed joints, concentrations of the drug approach serum levels.

Excreted by the kidneys, with 90% of renal elimination occurring via tubular secretion and 10% by glomerular filtration.

Probenecid blocks tubular secretion and has been used to increase the serum concentration and prolong the half-life of penicillin G and other penicillins.

**Clinical uses of penicillin G**

endocarditis caused by S. viridans (or Streptococcus bovis), pharyngitis

(group A β-hemolytic streptococci), cat bite cellulitis (Pasteurella multocida), and syphilis (Treponema pallidum).

**Dose;** 50,000 iu /kg-100,000iu/kg per dose 6hrly max 2.4g and bd in neonates up to 7days old.

C/I penicillin allergy

**The adverse effects of penicillins**

* Allergic reactions to penicillin are immediate immunoglobulin (Ig) E–mediated type I immune responses. s/s include urticaria, pruritus, bronchospasm, angioedema, laryngeal edema, and hypotension.
* Anaphylaxis (in approximately 1 in 100 000 injections);
* rashes (3–5% of patients) can, rarely, be severe (e.g. Stevens–Johnson syndrome
* serum sickness – type III hypersensitivity;
* Other idiosyncratic reactions including haemolytic anaemia and thrombocytopenia; in renal failure, high-dose penicillin causes encephalopathy and seizures.

**Limitations of benzylpenicillin** include:

* It is acid labile and so must be given parenteral (inactivated in gastric acid).
* It has a short half-life, so frequent injections are required.
* Development of resistant β-lactamase-producing strains can occur.
* It has a narrow spectrum/ treats infections caused by susceptible bacteria e.g gram +ve.

c/I ; patients with allergy to penicillins

**2) Benzathine penicillin** AND **procaine penicillin**

Depot iM formulations of penicillin G; have decreased solubility, delayed absorption, and a prolonged half-life. Drug concentrations are detectable 24 hours after injection of procaine penicillin

**Clinical use**; rheumatic fever prophylaxis.

**3) phenoxymethyl penicillin (Penicillin V** )is an orally having an antibacterial spectrum of activity that is similar to that of penicillin G. treat streptococcal infections when oral therapy is appropriate and desirable. DOSE; PO 500 mg qid

**Excretion**

By the kidneys, with 90% of renal elimination occurring via tubular secretion and 10% by GF. Probenecid blocks tubular secretion and has been used to increase the serum concentration and prolong the half-life of penicillin G and other penicillins.

**The clinical uses**

Endocarditis caused by *S. viridans* (or *Streptococcus bovis*), pharyngitis (group A β-hemolytic streptococci), cat bite cellulitis (*Pasteurella multocida*), and syphilis (*Treponema pallidum*).

**Adverse effects**

Allergic reactions e.g itching, eczematous rash, fever and angioneurotic edema rarely anaphylactic shock. Others include diarrhea due to altered normal flora, may lead to OI with pseudomonads or candida albicans, neutropenia

**b) Antistaphylococcal (penicillinase resistant) Penicillins**

Nafcillin, oxacillin, cloxacillin, and dicloxacillin;

Therapy for more resistant bacterial beta-lactamases than is penicillin G. Effective against streptococci and most community-acquired penicillinase- producing staphylococci.

MRSA (methicicllin resistant staph aureus ) strains do not respond to flucloxacillin so do Culture/Sensitivity or use clindamycin,tetracycline, trimethoprim. No renal adjustment required. N/B; MRSA and methicillin- resistant, Staphylococcus epidermidis (MRSE).

These nosocomial pathogens are resistant in vitro to all beta-lactam antibiotics.

**PK**

these drugs undergo hepatic metabolism, only nafcillin requires dose adjustment in patients with

combined hepatic and renal insufficiency.

Nafcillin IM, IV t1/2=0.8–1.2, renal excretion31–38%

Oxacillin IM, IV t1/2=0.4–0.7 renal excretion 39–66

Cloxacillin Oral t1/2=0.5–0.6 renal excretion 40–70

Dicloxacillin Oral t1/2=0.6–0.8 renal excretion 35–90

**Indications for use**

Severe staphylococcal aureus infections like cellulitis, empyema, endocarditis, osteomyelitis, pneumonia, septic arthritis, and toxic shock syndrome.

**BROAD SPECTRUM**

They are semi synthetic penicillin’s active against gram +ve and gram \_ve cocci

1) **Aminopenicillins**

**pharmacokinetics**

 **The ampicillin** and **amoxicillin** pk are similar. t1/2=1hr

Both have good oral bioavailability; ampicillin is also bioavailable after i.m injection. Oral doses of ampicillin should be given on an empty stomach because ingestion of food decreases the bioavailability of ampicillin but not amoxil. Ampicillin achieves therapeutic concentrations in the CSF only during inflammation.

**Ampicillin** is effective treatment for meningitis caused by Listeria monocytogenes., enterococcal endocarditis and pneumonia caused by b-lactamase-negative H. influenzae. Ampicillin Oral, IM, IV, t1/2=1.1–1.5, renal excretion 40–92% adjust dose in renal impairment.

**Amoxicillin** does not reach adequate concentrations in the CNS thus not appropriate for meningitis therapy. Oral, t1/2=1.4–2.0 excretion 86% renal adjust dose.

Antipseudomonal

**Uses**;

* Amoxicillin susceptible infections (including urinary-tract infections, otitis media, sinusitis, uncomplicated community acquired pneumonia, salmonellosis, oral infections).children 40mg-45mg/kg bd
* multidrug regimens for eradication of Helicobacter pylori in DU and PUD 1g bd.
* Anthrax (treatment and post-exposure prophylaxis) 80 mg/kg day in 3 divided doses Dental abscess (short course) Adult: 3 g, then 3 g after 8 hours
* Urinary-tract infections (short course) Adult: 3 g, then 3 g after 10–12 hours
* Listerial meningitis (in combination with another antibiotic) iv 2 g every 4 hours
* Endocarditis (in combination with another antibiotic ) Adult: iv. 2 g every 4 hours
* Prevention of pneumococcal infection in asplenia or in patients with sickle-cell disease—if cover also needed for Haemophilus influenza

**General cautions with ampicillin**; Acute lymphocytic leukaemia, chronic lymphocytic leukaemia, cytomegalovirus infection and glandular fever 🡺erythematous rashes

 **β*-Lactamase Inhibitor Combinations***

**Co –amoxiclav/ augmentin (amoxicillin 500mg + clavulanic acid 125mg ]).250/125mg oral and inj. 1g+ 200mg, ticarcillin-clavulanic acid [Timentin], piperacillin- tazobactam [Zosyn]**

An inhibitor of beta lactamases.

Preparations tabs, susp, injection vials.

augmentin ; a beta lactam combined with clavulanic acid. Elimination of the combination drugs is by renal excretion. Has good oral bioavailability.

antibacterial activity against β-lactamase-producing organisms.

**clinical use**

Treating infections with known or suspected mixed bacterial flora, like biliary infections, diabetic foot ulcers, endomyometritis, and peritonitis.

**Side effects**; cholestatic jaundice in elderly, hypersensitivity reactions.

I**ndications and dose**

* Infections due to beta-lactamase-producing strains (where amoxicillin alone not appropriate), e.g respiratory tract infections, bone and joint infections, genito-urinary and abdominal infections, cellulitis and animal bites 30mg/kg.
* Surgical prophylaxis iv,infusion Adult: 1.2 g, to be administered up to 30 minutes before the procedure, then 1.2 g every 8 hours for up to 2–3 further doses in high risk procedures
* Acute sinusitis (doses for 125/31 suspension) po 1–11 months: 0.25 mL/kilogram 3 times a day for 5 days alternatively 0.25 mL/kilogram 3 times a day for 5 days
* Acute sinusitis (doses for 250/62 suspension) Adult: 500/125 mg 3 times a day for 5 days

**flucloxacillin (amoxil +cloxacilin)**

Infections due to beta-lactamase-producing staphylococci including otitis externa , Adjunct in pneumonia , Adjunct in impetigo , Adjunct in cellulitis, bacterial endocarditis, surgical prophylaxis, staph. aureus infection.

**dose**; 25-50mg/kg bd neonates max 1g, osteomyelitis 100mg/kg

 **Indications and dose**

* Infections due to beta-lactamase-producing staphylococci including otitis externa Adjunct in pneumonia | Adjunct in impetigo | Adjunct in cellulitis

By mouth Child 1 month–1 year: 62.5–125 mg 4 times a day, Child 2–9 years: 125–250 mg 4 times a day, Child 10–17 years: 250–500 mg 4 times a day

Adult: 250–500 mg 4 times a day, I.m Adult: 250–500 mg every 6 hours, by slow iv or infusion Adult: 0.25–2 g every 6 hours

* Endocarditis (in combination with other antibacterial if necessary) by slow iv, or by intravenous infusion; Adult (body-weight up to 85 kg): 8 g daily in 4 divided doses, Adult (body-weight 85 kg and above): 12 g daily in 6 divided doses
* Osteomyelitis slow iv, OR iv infusion Adult: Up to 8 g daily in 3–4 divided doses
* Surgical prophylaxis; Adult iv infusion: 1–2 g, to be administered up to 30 minutes before the procedure, then (po or by i.m or by slow iv or by intravenous infusion) 500 mg every 6 hours if required for up to 4 further doses in high risk procedures
* Staphylococcal lung infection in cystic fibrosis Child: 25 mg/kg 4 times a day (max. per dose 1 g), alternatively 100 mg/kg daily in 3 divided doses; maximum 4 g per day
* Prevention of Staph. aureus lung infection in cystic fibrosis—primary and secondary prevention

**C/I and precaution**

Cholestatic jaundice and hepatitis may occur very rarely, up to two months after treatment with flucloxacillin has been stopped.

it not be used in patients with a history of hepatic dysfunction associated with flucloxacillin and be used with caution in patients with hepatic impairment

**2) Antipseudomonal Penicillins**

**Carbenicillin Oral ,Mezlocillin, piperacillin, and ticarcillin iv, i.m.**

The carboxypenicillin like ticarcillin is indicated for serious infections caused by pseudomonous aruginosa and G-ve bacilli like proteus and bacteroids.

pk; During their distribution phase, antipseudomonal penicillins achieve only low concentrations in the CSF thus not the drugs of first choice for meningitis therapy **mezlocillin**;Has hepatic metabolism needs adjustment in patients with hepatic insufficiency.

adjust dose in renal disease for all drugs

Carbenicillin Oral , t1/2=0.8–1.2, 85%

Mezlocillin IM, IV, t1/2= 0.9–1.7, 61–69%

Piperacillin IM, IV t1/2=0.8–1.1, 74–89 %

Ticarcillin IM, IV ,t1/2=1.0–1.4 ,95%

**ticarcillin** is combined with clavulanic acid as a 3.2g powder inj.for reconstitution. n/b dose check with manufacture information.

Antibiotics formulated as sodium salts. Precaution in patients with CCF.

**clinical use**Pneumonias associated with cystic fibrosis or mechanical ventilation.

**SIDE-EFFECTS**

Common or very common Anaemia . candida infection . constipation . gastrointestinal discomfort . headache . insomnia

Uncommon; Arthralgia . flushing . hypokalaemia . hypotension . myalgia

Rare or very rare Epistaxis . stomatitis positive, urine glucose on lab urinalysis

|  |  |  |  |
| --- | --- | --- | --- |
| **Week 3** |  |  | Cephalosporins, carbapenems, monobactams |

1. **cephalosporins (2hrs)**

The cephalosporins are semisynthetic antibiotics derived from Cephalosporium and Streptomyces, broad-spectrum antibiotics

**MOA**;antibacterials that attach to penicillin binding proteins to interrupt cell wall biosynthesis, leading to bacterial cell lysis and death.

**clinical uses**; septicaemia, pneumonia, meningitis, biliary-tract infections, peritonitis, and urinary tract infections.

The pharmacology of the cephalosporins is similar to that of the penicillins, excretion being principally renal. Penetrate the CSF poorly unless the meninges are inflamed; cefotaxime and ceftriaxone are suitable cephalosporins for infections of the CNS (e.g meningitis).

 **side-effectS**;

The **principle** S.E is hypersensitivity and about 0.5–6.5% of penicillin-sensitive patients will also be allergic to the cephalosporins

Common or v**ery common**;

Abdominal pain . diarrhoea . dizziness . eosinophilia . fungal infection . headache . leucopenia . nausea . neutropenia . skin reactions .thrombocytopenia . vomiting

U**ncommon** Anaphylactic reaction ,antibiotic associated colitis

Rare or very rare; Agranulocytosis . angioedema . haemolytic anaemia . nephritis tubulointerstitial (reversible) . severe cutaneous adverse reactions (SCARs)

**Classified into generations 1st ,2nd ,3rd ,4th** (see the above table) and According to their antibacterial spectrum and stability to beta-lactamases.

**First generation**; UTI **which do not respond to other drugs or which occur in pregnancy, RTI, otitis media, and skin and soft-tissue infections.**

Cefadroxil ---Oral---- t1/2=1.2–2.5hrs –->25mg/kg in two divided doses. adults 500mg-1g bd

Cefazolin ------IM, IV -- t1/2=1.5–2.5 hrs

Cephalexin ----Oral--- t1/2=1.0 hrs-🡪25mg/kg/d in two or three divided doses adult 500mg-1g bd

Cephapirin ----IM, IV--- t1/2=0.6 hrs

Cephradine ----Oral ---t1/2=0.7 hrs

**Second generation🡪h.influenza,neiseria gonococci meningitis, UTI, prophylaxis for surgery ,open fractures, pyelonephritis**

Cefaclor- Oral 20mg/kg/d in 2-3 divided doses -----t1/2=0.6–0.9 hrs

Cefamandole--- IM, IV-- t1/2=0.5–1.2 hrs

Cefmetazole—IV-- t1/2= 1.2–1.5 hrs

Cefonicid ------IM, IV-- t1/2= 3.5–4.5 hrs

Cefotetan-- ---IM, IV --t1/2=2.8–4.6 hrs

Cefoxitin ----IM, IV-- t1/2= 0.7–1.0 hrs

Cefprozil ----Oral ------t1/2=1.2–1.4 hrs

Cefuroxime ( zinacef) --IM, IV-- 1.1–1.3 hrs🡪60mg/kg/day -100mg/kg/d 8 hrly

Cefuroxime (axetil)–Oral, ---t1/2=1.1–1.3 hrs 🡪10mg-15mg/kg/d or 250-500mg bd

Loracarbef*a –*Oral--- t1/2= 1.0 hrs

**Third generation🡪 serious septicaemias,pneumonias,menengitis**

Cefdinir ---Oral----- t1/2= 1.7 hrs

Cefixime--- Oral--- t1/2= 2.3–3.7 hrs 🡪8mg/kg/d bd 10yrs-adult 200-400mg bd

Ceftriaxone------- IM, IV---- t1/2=5.8–8.7 hrs50-100mg/kg/ daily

Cefoperazone-- IM, IV---t1/2= 2.0 hrs

Cefotaxime ---IM, IV--- t1/2=1.0 hrs🡪50mg-100mg/kg/d in 2-4 divided doses

Cefpodoxime proxetil ----Oral-- 1.9–3.7 hrs🡪 4mg/kg/d 12hly

Ceftazidime---- IM, IV--- t1/2= 1.9 hrs 🡪30-100mg/kg/day in two divided max 6g

Ceftibuten ---Oral--- t1/2= 1.5–2.8 hrs

Ceftizoxime------ IM, IV---- t1/2= 1.4–1.8 hrs

**4th gen**

Cefepime ---IM, IV----t1/2= 2.0 hrs

**5TH Gen**

Ceftaroline fosamil; iv infusion

Community-acquired pneumonia; Adult: 600 mg every 12 hours for 5–7 days

Complicated skin infections , Complicated soft-tissue infections

Adult: 600 mg every 12 hours for 5–14 days

**PK** Most parenteral cephalosporins have good bioavailability after i.m injection.

The cefuroxime axetil (Ceftin) and cefpodoxime proxetil (Vantin) are oral formulation. Concomitant ingestion of food reduces the bioavailability of some cephalosporins, e.g., cefaclor (Ceclor), and therefore, should be administered on an empty stomach.

Cefadroxil has a long duration of action and given bid daily; it has poor activity against H. influenzae. Cefuroxime axetil, an ester of the ‘second generation’ cephalosporin cefuroxime, has the same antibacterial spectrum as the parent compound; it is poorly absorbed thus needs to be given with food to maximize absorption.

Only cefepime, cefuroxime (Zinacef), cefotaxime (Claforan), ceftriaxone (Rocephin), and ceftazidime (Fortaz) achieve therapeutic concentrations in CSF thus used in empirical treatment of brain abscess and meningitis

N/B; Ceftriaxone has protein binding (85–95%) may displace **bilirubin** from serum albumin. Consequently increasing the risk of kernicterus in **jaundiced neonates**. can worsen acidosis. Excretion -urinary

**Clinical Uses**

* The first-generation cephalosporins are useful in antimicrobial prophylaxis before surgery. 2nd-generation cephalosporins are used to treat infections caused by susceptible organisms.
* Cefoxitin and cefotetan have good anaerobic activity thus treatment and prophylaxis of lower abdominal and gynecological infection.
* 3rd generation for wide range of infections like pneumonia, meningitis,peritonitis, and sepsis syndrome.
* Ceftaroline fosamil is a ‘fifth generation’ cephalosporin with bactericidal activity similar to cefotaxime; has an extended spectrum of activity against Gram-pos. bacteria that includes meticillinresistant S. aureus and multi-drug resistant Streptococcus pneumoniae. treatment of community-acquired pneumonia and complicated skin and soft-tissue infections, but there is no experience of its use in pneumonia caused by meticillinresistant S. aureus.

**CAUTIONS;** Seizure disorders

**Side-effects; Anaemia . hypersensitivity**

**Adverse Effects**

The reactions are rashes (1–5%), eosinophilia (3–10%), gastrointestinal symptoms (3%), hematological abnormalities (1–2%), phlebitis (2%), and fever (1%). Anaphylactic

Because of cross-reactions between cephalosporins and penicillins, caution should be used when prescribing cephalosporins to patients with penicillin allergy. Thrombocytopenia -reduced prothrombin concentration and bleeding has been described.

Some first-generation cephalosporins are nephrotoxic, particularly if used with furosemide, aminoglycosides or other nephrotoxic agents.

Some of the 3rd gen drugs are associated with bleeding due to increased prothrombin times, which is reversible with vitamin K.

**Ceftriaxone im,iv, infusion**

**Indications and dose**

* Community-acquired pneumonia, Hospital-acquired pneumonia, Intra-abd. infections.
* urinary-tract infections ,Acute exacerbations of chronic obstructive pulmonary disease

Adult: 1–2 g once daily, 2 g dose to be used for hospital-acquired pneumonia and severe cases

* Complicated skin and soft tissue infections , Infections of bones and joints Adult: 2 g once daily
* Suspected bacterial infection in neutropenic patients Adult: 2–4 g daily.
* Bacterial meningitis
* Bacterial endocarditis ; Adult: 2–4 g daily.

Child 1 month–11 years (body-weight up to 50 kg): 80–100 mg/kg once daily, 100 mg/kg once daily dose should be used for bacterial endocarditis; maximum 4 g per day

Child 9–11 years (body-weight 50 kg and above): 2–4 g once daily

Child 12–17 years: 2–4 g once daily.

* Surgical prophylaxis ; Adult: 2 g for 1 dose, dose to be administered 30–90 minutes before procedure
* Uncomplicated gonorrhoea , Pelvic inflammatory disease; Adult: 500 mg for 1 dose
* Syphilis; Adult: 0.5–1 g once daily for 10–14 days, dose increased to 2 g once daily for neurosyphilis
* Disseminated Lyme borreliosis (early [Stage II] and late [Stage III]); Adult: 2 g once daily for 14–21 days, the recommended treatment durations vary and national or local guidelines should be taken into consideration
* Prevention of secondary case of meningococcal meningitis Adult: 250 mg for 1 dose
* Prevention of secondary case of Haemophilus influenza type b disease Adult: 1 g daily for 2 days
* Acute otitis media; Adult: 1–2 g for 1 dose, dose can be given for 3 days if severely ill or previous therapy failed
1. **carbapenems and carbacephems ( iv)**

The newest classes of beta -lactam and broad spectrum antibiotics g-ve and g +ve organisms

**Meropenem; IV Infusion or iv in 5% dextrose or N/S =20mg/ml over 30min**

The first carbapenem is Meropenem (Merrem )

**Indications and dose**

Aerobic and anaerobic Gram-pos and Gram-neg infections Hospital-acquired septicaemia Adult: 0.5–1 g every 8 hours.

Exacerbations of chronic lower r/s infection in cystic fibrosis Adult: 2 g every 8 hours

Meningitis; Adult: 2 g every 8 hours

Endocarditis (in combination with another antibacterial ; Adult: 2 g every 8 hours

child; 25-40mg/kg tid

**side-effects**

Common or very common ;Abdominal pain . diarrhoea . headache . inflammation . nausea . pain skin reactions . thrombocytosis . vomiting

 Agranulocytosis . antibiotic associated colitis . eosinophilia . haemolytic anaemia . increased risk of infection . leucopenia . neutropenia . paraesthesia . severe cutaneous adverse reactions (SCARs) . thrombocytopenia

**Imipenem with cilastatin ( iv infusion) (*Primaxin***)

It’s a chemically stable analogue of thienamycin produced by Streptomyces cattleya. It is partially inactivated within the kidney and is thus co-formulated with cilastatin, which blocks this renal metabolism. Imipenem-cilastatin IM, IV--- t1/2= 1 hr.

Active against most gram-positive, gram negative and anaerobic bacteria. More potent than 3rd gen cephalosporins. Active against E. faecalis, B. fragilis, and P. aeruginosa.

**Indications and dose**

* Aerobic and anaerobic Gram+ve and Gram-neg infections (not indicated for CNS infections) Hospital acquired septicaemia Adult: 500 mg every 6 hours, alternatively 1 g every 8 hours
* Infection caused by Pseudomonas or other less sensitive organisms (Pulmonary, intraabdominal and soft tissue infections).
* Empirical treatment of infection in febrile patients with neutropenia
* Life-threatening infection ; Adult: 1 g every 6 hours DOSE **expressed in** terms of imipenem.

**CAUTIONS CNS** disorders . epilepsy

**side-effects**

Common or very common; Diarrhoea . eosinophilia . nausea . skin reactions . vomiting

Uncommon; Bone marrow disorders . confusion . dizziness . drowsiness . hallucination . hypotension . leucopenia . movement disorders . psychiatric disorder . seizure thrombocytopenia . thrombocytosis, Positive Coombs’ test.

**ADR**

Diarrhoea . headache . nausea .vomiting

Seizures in 1% of patients. Risk factors for old age, head trauma, previous seizure disorder, cerebrovascular accident, and renal failure. git symptoms, hearing loss, taste disturbance, blood disorders, positive coombs test, allergic reactions plus steven johnsons rash, epidermal necrosis

History of penicillin allergy, 10% are cross- sensitive

**Ertapenem;** **iv infusion**

For treating abdominal and gynaecological infections and for community-acquired pneumonia, but it is not active against atypical respiratory pathogens and it has limited activity against penicillin resistant pneumococci. Unlike the other carbapenems, ertapenem is **not** active against Pseudomonas or against Acinetobacter spp.

**indications and dose**

* Abdominal , Acute gynaecological infections ,Community-acquired pneumonia iv infusion Adult: 1 g once daily
* Diabetic foot infections of the skin and soft-tissue ;iv infusion 1 g once daily
* Surgical prophylaxis, colorectal surgery Adult: 1 g for 1 dose, dose to be completed within 1 hour before surgery

**CAUTIONS** CNS disorders—risk of seizures . elderly

Allergy and cross-sensitivity ;avoid if history of hypersensitivity reaction to beta-lactams.

Use with caution in patients with sensitivity to betalactam antibacterials.

Pregnancy Manufacturer advises void unless potential benefit outweighs risk.

Breast feeding Present in milk—manufacturer advises avoid.

**N/B**; **assignment** -*read on individual drugs dosages as prescribed clinically( units/kg or mg/kg )check out in the drug index book.*

1. **Monobactams.**

**aztreonam (Azactam) 30-50mg/kg 8hrly )** **I.V, I.M.**

**Pharmacokinetics**

They are the monocyclic beta-lactams contain a 5-monobactam ring and are resistant to β-lactamase degradation.

Has excellent activity against gram-negative organisms, including P. aeruginosa.

Has low affinity for penicillin-binding proteins in streptococci, staphylococci, and anaerobes and therefore has no significant activity against gram-positive bacteria or anaerobes.

During its distribution phase, the drug can achieve therapeutic concentrations in cerebrospinal for the therapy of meningitis caused by gram-negative bacilli. C/I pregnancy and hypersensitivity

Aztreonam is poorly absorbed after oral administration, so it is given parenterally.

It is widely distributed to all body compartments, including the cerebrospinal fluid. Excretion is renal and the usual half-life 1-2hours) is increased in renal failure.

**Clinical uses**

Its an alternative to an aminoglycoside, severe sepsis, often hospital acquired, especially infections of the respiratory, urinary, biliary, gastro-intestinal and female genital tracts.

N/B; It has a narrow spectrum of activity and cannot be used alone unless the organism’s sensitivity to aztreonam is known.

|  |  |  |  |
| --- | --- | --- | --- |
| **Week 4** |  |  | Drugs that inhibit nucleic acid synthesis - sulphonamides &trimethoprim, nitroimidazoles, quinolones |

**Quinolones and Nitrofurans (2hr)**

**Examples of quinolones**

* Cinoxacin
* Ciprofloxacin
* Enoxacin
* Norfloxacin
* Ofloxacin
* Gatifloxacin
* Levofloxacin
* Lomefloxacin
* Moxifloxacin
* Nalidixic acid

**Nitrofuran**

1. Nitrofurantoin
2. Nitrofurazone

**QUINOLONES/ FLUOROQUINOLONES AND NALIDIXIC ACID**

Chemistry and MOA

The 4- quinolones inhibit DNA synthesis of bacteria through their specific action on DNA gyrases, which are composed of two A and two B subunits. The A subunits are the site of action for the 4-quinolones.

Recently a second target, unique to the fluoroquinolones, has been identified as topoisomerase type IV. The effect of quinolones on these DNA enzymes is initially bacteriostatic but becomes bactericidal when bactera are unable to repair the DNA lesions. **Nalidixic acid is the first** quinolone, has been available for 30 years.

**Pk of quinolones**

* The quinolones are rapidly and almost completely absorbed after oral administration and widely distributed in body tissues.
* Ciprofloxacin and ofloxacin have been detected in breast milk and ofloxacin levels in ascites fluid are close to serum levels.
* Food ingestion does not affect bioavailability, which ranges from 50 to 95%.
* The plasma t1/2= 3 - 4 hrs.
* Elimination is via glomerular filtration and tubular secretion. Dosages are modified in renal insufficiency. They are metabolized by hepatic conjugation and glucuronidation. **Caution** should be observed with administration of trovafloxacin because of its potential to induce hepatic toxicity.

N/B Dosage, peak serum levels, percent protein binding, urine concentrations, and degree of metabolism differ to varying degrees among the quinolones.

**Classified into generations**

1st to 4th , has spectrum specificity and unique pharmacological properties, although there is considerable overlap:

1st generation- **nalidixic acid** and **cinoxaci**n;

2nd generation -n**orfloxacin**, **ciprofloxacin**, **ofloxacin**, **enoxacin**, and **lomefloxacin**

3rd generation--**levofloxacin**, **sparfloxacin**, **gatifloxacin**;

4th generation - t**rovafloxacin** and **moxifloxacin**.

Several of the newer quinolones have been recently removed

**Antibacterial Spectrum and Resistance**

**Nalidixic acid and cinoxacin; PO**

**The 1st –gen**. and oldest quinolones exhibit limited gram-negative activity.

They are bactericidal agents BUT restricted due to resistance

Administered orally, it achieves low tissue concentrations are thus restricted to therapy of bladder infections caused by urinary pathogens, such as E. coli and Klebsiella and Proteus spp.

**The 2nd –generation**; Active against gram-negative organisms, including Enterobacteriaceae. Haemophilus spp. and sexual infections (STD) agents, such as Neisseria gonorrhoeae, Chlamydia trachomatis, Urea plasma urealyticum, and Moraxella catarrhalis (formerly Neisseria catarrhalis; causes otitis media)

The antipseudomonal activity of ciprofloxacin, norfloxacin, ofloxacin, and lomefloxacin is due to their piperazine moiety. Active against gram-positive organisms, such as S. pneumoniae, is demonstrated the third and fourth generations.

Ciprofloxacin covers for Bacillus anthracis. A major Resistance is related to mutations in the DNA gyrase, with the gyrase gene A (gyrA) being the predominant site.

Methicillin-resistant Staphylococcus aureus and Enterococcus faecium are **resistant**.

**Pharmacokinetics Of ciprofloxacin**

It is well absorbed after PO and is distributed rapidly into body tissues. Most of the drug is eliminated unaltered by the kidneys; the remainder is excreted by hepatic metabolism or unchanged in the faeces.

**Adverse effects**

* The ADR are minor GIT upsets; nausea, vomiting, diarrhea, and abdominal pain.
* CNS disturbances; insomnia, drowsiness, weakness, headache, dizziness, confusion and convulsions, psychosis.
* Artyhralgia; Can damage cartilage in young animals, ciprofloxacin is c/I in children and growing adolescents.
* Vision disturbances
* Allergic reactions e.g., rashes, urticaria, and eosinophilia.
* cholestatic jaundice
* blood dyscrasias, hemolytic anemia,
* hypoglycemia
* nephrotoxicity.

**Drug interactions**

Its absorption is reduced significantly by the co-administration of aluminium and magnesium antacids. there is chalation

 It interferes with the metabolism of theophylline, caffeine and warfarin and so -> toxic effects

**Doses for 2nd generation**

nofloxacin; 400mg bd x 3- 7 days for UTI.

ciprofloxacin: po,iv; 250–750 mg 12-hourly or 15mg/kg /day ; i.v:200–400 mg 12-hourly.

Ofloxacin po,iv ; 200-400mg/day x 7 days ; **SE** cough ,hypotension, anxiety, unsteady gait, psychosis, Acute kidney injury, enterocolitis, hot flush . nightmare . respiratory disorders

**3rd generation;** **levofloxacin, sparfloxacin, gatifloxacin**

Levofloxacin has similar spectrum to ciprofloxacin but much greater activity against *S. pneumoniae.*

**Levofloxacin po, iv;**

**INDICATIONS AND DOSE**

* Acute sinusitis; po: 500 mg once daily for 10–14 days
* Acute exacerbation of chronic bronchitis po: 500 mg once daily for 7–10 days
* Community-acquired pneumonia po 500 mg od/bd day for 7–14 days, iv 500 mg od/bd day, to be given over at least 60 minutes
* other indications as above e.g skin infections, anthrax prophylaxis, chronic pneumonias ,cystic fibrosis by p. auruginosa, chronic prostatitis, Uti.

**ADR**

photosensitivity, correlate with specific chemical structures, including the halogen substitutionon the eighth position, as found in sparfloxacin and lomefloxacin.

vascular embolism, cardiac insufficiency, hypotension

Dose of levofloxacin Oral and i.v: 500–750 mg once daily for 7 days

**The 4th -gen quinolones** also possess activity against anaerobes; -Trovafloxacin and moxifloxacin.

**Dose and indications;**

moxifloxacin (avelox, peflox) 400mg od for 10/7 for CAP pneumonias, sinusitis and bronchitis. PID – treat for 14 days.

Complicated skin and soft-tissue infections which have failed to respond to other antibacterials or for patients who cannot be treated with other antibacterials; Adult: 400 mg once daily for 7–21 days

**ADR**;

Can exacerbate QT prolongations.

Fulminant hepatotoxicity associated with trovafloxacin has resulted in acute liver failure, and the FDA has recommended limiting therapy to life-threatening infections.

**Caution**;

With trovafloxacin because it induces hepatic toxicity. hx of epilepsy they induce seizures, g6pd deficiency, myasthenia gravis, arthralgia in wt bearing joints in pts and children as they damage the cartlages and tendons , pregnancy, breast feeding

**Clinical Uses of fluoroquinolones**

* Therapy for; UTI and RTI, GI and abdominal infections, STDs, and bone, joint and soft tissue infections. Fistulating Crohn’s disease
* po ciprofloxaxin; Adult: 500 mg twice daily Respiratory-tract infections
* Pseudomonal lower respiratory-tract infection in cystic fibrosis
* Urinary-tract infections
* Acute uncomplicated cystitis in women po Adult: 250 mg twice daily for 3 days
* Acute or chronic prostatitis; po 500 mg bd daily for 28 daysiv; Adult: 400 mg every 8–12 hours, to be given over 60 minutes
* Gonorrhoea; Adult: 500 mg for 1 dose
* Most other infections po Adult: Initially 500 mg twice daily; increased to 750 mg twice daily, in severe or deep-seated infection iv Adult: 400 mg every 8–12 hours, to be given over 60 minutes
* Surgical prophylaxis; p.o Adult: 750 mg, to be taken 60 minutes before procedure
* Anthrax (treatment and post-exposure prophylaxis) Adult: 500 mg twice daily
* The 2nd -generation fluoroquinolones are all equally efficacious in UTIs, efficacy in treating prostatitis.
* The 3rd - and 4th -generation fluoroquinolones are more effective in treating Community Aquired Pneumonias because of their activity against S. pneumonia, nosocomial pneumonia, chronic bronchitis (acute exacerbations), skin infections and chronic otitis media.
* Treats GI infections, including traveler’s diarrhea due to E.coli, shigellosis, and typhoid fever.
* Primary cervicitis, urethritis, and pelvic inflammatory disease due to the STD agents N. gonorrhoeae and C. trachomatis.
* ciprofloxacin ; Prevention of secondary case of meningococcal meningitis; po

Child 1 month–4 years: 30 mg/kg (max. per dose 125 mg) for 1 dose

Child 5–11 years: 250 mg for 1 dose

Child 12–17 years: 500 mg for 1 dose

Adult: 500 mg for 1 dose

**Note;** fluoroquinolones are contraindicated in the treatment of enterohemorrhagic E. coli because they can induce the cytotoxic Shiga-like toxin. Ciprofloxacin and ofloxacin are ineffective against Treponema pallidumm but are active against the less common Haemophilus ducreyi.

**Drug interactions**

Co-administration of **ciprofloxacin** and **theophylline** causes elevated blood **theophylline** concentrations due to inhibition of cytochrome P450. As both drugs are epileptogenic, this interaction is particularly significant

**CONTRAINDICATIONS**

Pregnant women, breast feeding, young growing children, patients with history of tendon disorders, over 60yrs.

**Sulfonamides (2hr)**

These are synyhetic organic compounds

Sulfamethoxazole and trimethoprim are used in combination (as co-trimoxazole) because of their synergistic activity.

Chemistry, Structure, and Function

The sulfonamides are a large group of compounds that are structural analogues of *p-*aminobenzoic acid (PABA).

**P.K**

Sulfonamides are usually given orally, although the soluble sodium salts can be given parenterally, infrequently used. Some sulfonamide remains unabsorbed in the (GI) tract following oral administration. They produce changes only on local gut bacterial flora and finds wide use in presurgical bowel sterilization. Sulfisoxazole is rapidly absorbed and highly soluble. sulfamethoxazole is rapidly absorbed and slowly excreted and maintain adequate blood levels for up to 24 hours thus useful in treating chronic urinary infections.

They distribute throughout body fluids. e.g placental barrier and enter CSF even in the absence of inflammation. Some sulfonamides (e.g., sulfacetamide and sulfadiazine [silver salt]) are designed for topical use such as in infection of the eye and in burn patients. t 1/2= 2.5 -17 hrs.

Metabolism and Excretion-They are degraded in the liver by acetylation and oxidation. Sulphonamides are oxidants and can precipitate haemolytic anaemia in glucose-6-phosphate dehydrogenase (G6PD)-deficient individuals. The parent compound and the metabolites are excreted in the urine.

**Drug interactions**

The sulphonamide component competes for hepatic enzyme-binding sites and can decrease the clearance of phenytoin, tolbutamide and warfarin sufficiently to produce phenytoin toxicity, hypoglycaemia and enhanced anticoagulation, respectively.

Displacement of methotrexate from protein-binding sites can also lead to toxicity.

**Examples of sulphonamides**

1. Sulfamethoxazole
2. Sulfadiazine (silver)
3. Sulfamerazine
4. Sulfamethazine
5. Sulfisoxazole
6. Trimethoprim sulfadoxine) + pyrimethamine (Fansidar)
7. Trimethoprim–sulfamethoxazole ( Septrin, Bactrim*)PO,IV*

**Mechanism of Action and Resistance**

They are bacteriostatic drugs.

They reversibly block the synthesis of folic acid useful for bacterial growth.

Humans cannot synthesize folic acid and must acquire it in the diet; thus, they selectively inhibit microbial growth by interfering with folic acid synthesis by bacteria. Their structural analogues competitively block PABA incorporation into dihydropteroic acid, an intermediate compound in the formation of folinic acid.

**Antibacterial spectrum**

They are broad-spectrum antimicrobials , effective against gram-positive *Neisseria gonorrhoeae*, *H. influenzae* and some gram-negative organisms of the Enterobacteriaceae, E.coli, moderate activity and against Proteus mirabilis and Enterobacter spp. Toxoplasma gondii and occasionally chloroquine resistant Plasmodium falciparum or malaria prophylaxis in preg. women.

**Trimethoprim**

it’s well absorbed, highly lipid soluble and widely distributed.

65% is eliminated unchanged in the urine.

Competes for the same renal clearance pathway as creatinine.

It is well tolerated.

**Side effects**

GIT disturbances, skin reactions and Bone M depression.

The high doses used in management of PCP in immunosuppressed patients, causes vomiting (mx by prophylactic anti-emetics), serious skin reactions, hepatitis and thrombocytopenia.

**Dose**; Child; 2- 4 mg/kg twice daily (max. per dose 200 mg) adults 200mg bd

Treatment of mild to moderate Pneumocystis jirovecii (pcp) in patients who cannot tolerate co-trimoxazole (in combination with dapsone) Child and adult: 5 mg/kg every 6–8 hours

**Contra-I;** Blood dyscrasias. **Precaution**; g6pd deficiency , Teratogenic risk in first trimester (folate antagonist).

**Clinical Uses**  **of cotrimoxazole (sulfamethoxazole 400mg and trimethoprim 80 mg.)**

* They treat both gram-positive and gram-negative bacterial infections.
* They are also active as leprosy, malaria, toxoplasmosis
* Urinary tract and ear infections.
* Trimethoprim–sulfamethoxazole ( Septrin, Bactrim) is treatment of choice in both the treatment and prevention of infections caused by P. carinii, a protozoan that produces serious pneumonitis in patients with hematological malignancies and HIV/AIDS.

**Dosage** 960 mg (two tablets of 400 mg sulphamethoxazole, 80 mg trimethoprim) 12-hourly for oral or iv administration (children, 120–480 mg 12-hourly depending on age).

* treatment of (PCP) p.carinii; iv or po CTX 120mg/kg/day in 2-4 divided doses x 14/7
* Sulfadiazine and sulfisoxazole for the prophylaxis of group A streptococcal infections in patients with rheumatic fever who are hypersensitive to penicillin. dose; sulfadiazine 500mg for patients < 30kg and 1g daily for adults.
* Pyrimethamine, are considered the treatment of choice of symptomatic toxoplasmosis.
* Sulfonamide (sulfadoxine) + pyrimethamine (*Fansidar*) =malaria prophylaxis and treatment.
* Silver sulfadiazine in a 1% cream can be used as an alternative to mafenide and has good activity against gram-negative bacteria. Silver sulfadiazine in a 1%
* Cream can be used as an alternative to mafenide and has good activity against gram-negative bacteria. Active against *P*. aeruginosa that colonizes the burns.

**dosage of cotrimoxazole (sulfamethoxazole 400mg and trimethoprim 80 mg.)**

* Treatment of susceptible infections Child 6 weeks–5 months: 120 mg twice daily or 24 mg/kg twice daily
* Treatment of Pneumocystis jirovecii/PCP) infections (undertaken where facilities for appropriate monitoring available. po /iv Child: 120 mg/kg daily in 2–4 divided doses for 14–21 days, po preferred for children, Adult: 120 mg/kg daily in 2–4 divided doses for 14–21 days
* Prophylaxis of Pneumocystis jirovecii (Pneumocystis carinii) infections

po Child: 450 mg/m2 twice daily (max. per dose 960 mg bd daily) for 3 days of the week (either consecutively Adult: 960 mg once daily, reduced if not tolerated to 480 mg once daily, alternatively 960 mg once daily as above

**ADR**

* Hypersensitivity reactions (e.g., rashes, eosinophilia, and drug fever).
* Stevens-Johnson syndrome is also associated with sulfonamide use.
* Vasculitis, photosensitivity
* Blood dyscrasias, agranulocytosis, and thrombocytopenia, Eosinophilia, megaloblastic anaemia
* Hemolytic anemia may develop in persons with a genetic deficiency of red blood cell (glucose-6-phosphate dehydrogenase (G6PD).
* renal disorders; interstitial nephritis
* hyponatremia
* Epidermal necrosis.
* Hepatotoxicity especially with septrin.
* Kernicterus they compete for sites on plasma proteins that are responsible for the binding of bilirubin leading to less bilirubin is bound in the newborn, the unbound bilirubin deposits in the basal ganglia and sub-thalamic nuclei, causing kernicterus,a toxic encephalopathy. N/B sulfonamides should not be administered to newborns or to women during the last 2 months of pregnancy.
* Their use during pregnancy is usually C/I by the potential for effects on the fetus, such as the development of neural tube defects associated with folate deficiency.
* Long-term use of trimethoprim in persons with folic acid deficiency, such as alcoholics and the malnourished.

**Nitrofurans**

**(Nitrofurantoin) po tabs,nitrofurazole topical for trypanosomiasis,wounds**

**Chemistry and Mechanism of Action**

A number of 5-nitro-2-furaldehyde derivatives, used in the treatment and/or prophylaxis of microbial infections, primarily in the urinary tract, inhibits DNA, protein synthesis and cell wall synthesis.

It is presumed that the nitrofurans are selectively toxic to microbial cells because in humans, the slower reduction by mammalian cells prevents high serum concentrations.

**Antibacterial Spectrum and Resistance**

Active against gram-negative bacteria (E. coli, P. mirabilis is variable) and some susceptible gram-positive organisms, such as S. aureus and Enterococcus faecalis.

In vitro activity is demonstrated against Staph. saprophyticus and Staph. epidermidis.

**PK**;

* Orally it is rapidly and almost completely absorbed from the small intestine;
* Relatively high protein binding (about 70%) also affects serum levels, reducing potential for systemic toxicity and alteration of intestinal flora. has poor tissue penetration and low blood levels.
* Rapidly excreted by glomerular filtration and tubular secretion to yield effective urinary levels. The drug is inactivated in the liver. plasma t1/2= 30-60min. elimination t1/2 =20min.

**Dosage** > 3months old =po nitrofurantoin= 3mg/kg/day in 4 divided doses x 7 days.

Prohylaxis; 1mg /kg /day o.d at night or 50-100mg/day adults.

**Adverse Effects and Drug Interactions**

Nausea and vomiting. dyspesia

Pulmonary hypersensitivity reactions can result in chronic morbidity, usually after therapy lasting at least 6 months. Findings can include (chronic desquamative interstitial pneumonia with fibrosis.) peripheral neuropathy. Hair loss, allergic pruritus, dizziness, drowsiness

c/I; babies less than 1month🡪 hemolytic anaemia, preg in3rd preg ,G6PD defficiency

**n/b;** nitrofurans are mutagenic/carcinogenic and are no no-longer in use since 1991

**Other antibacterial drugs; NITROIMIDAZOLE DERIVATIVES/ AZOLES( 2hr)**

**Metronidazole and tinidazole**

**Metronidazole po,iv , suspension 200mg/5ml**

It is active against protozoal infections and anaerobic bacteria plus *B. fragilis* and *C. difficile* associated diarrhea and H-pylori

**Indications**

* Also combined with gentamicin and amoxicillin in treating intra-abdominal sepsis and peritonitis.
* Treating trichomonal vaginitis
* giardiasis
* ulcerative necrotizing gingivitis /Acute ulcerative gingivitis
* h- pylori clarithromycin and lansoprazole; or in combination with amoxicillin and lansoprazole
* combined with gentamicin as prophylaxis in abdominal surgery.
* Pelvic inflammatory disease po: 400 mg twice daily for 14 days
* Invasive intestinal amoebiasis/ Extra-intestinal amoebiasis (including liver abscess)
* Acute oral infections
* Surgical prophylaxis

**Tinidazole** t1/2=13hrs, **dose** 2g single dose for trichomonas and excreted unchanged in urine

**ADR**-The only major adverse effectsare peripheral neuropathy following prolongedtherapy and seizures following high doses. Others include; metallic taste, flurred tongue, dizziness, ataxia.

**Dose of metronidazole**

* For severe infections, i.v infusion of metronidazole -the rate of 500 mg every 8 hrs in adults. child 7.5mg/kg 8hrly
* Oral: 400 mg orally 8-hourly for serious bacterial infections. 200 mg 8-hourly for 7 days for trichomoniasis and 2 g daily for 3 days in amoebiasis and giardiasis.
* Dose: 1 g 8-hrly as Suppositories available.

**Tinidazole po** see above

Dose 2g stat for gingivitis and vaginitis

Anaerobic infections 2g o.d for 3days

C/I preg 1st tremister, porphria

|  |  |  |  |
| --- | --- | --- | --- |
| **Week 5:** |  |  | **Drugs that inhibit protein synthesis –aminoglycosides, chloramphenicol, clindamycin, fucidic acid**  |

**Aminoglycosides**

Chemical structure; Are hydrophilic, polycationic amine, containing carbohydrates usually composed of 3- 5 rings. Water soluble substance; do not easily cross cell membrane.

The polycationic structure 🡪 binding both to the anionic outer bacterial membrane🡪 bactericidal effects and to anionic phospholipids in the cell membranes of mammalian renal proximal tubular cells🡪 their toxicity.

Most of them are either natural products or derivatives of soil actinomycetes

Amikacin is more stable than gentamicin to enzyme inactivation. Thus used in treatment of serious infections caused by gentamicin-resistant Gram-negative bacilli.

**Drug examples are**;

1. **Amikacin;** iv.im 15mg/kg/day in 2 divided doses,
2. **gentamicin** –dose 3-7.5mg/kg/day, given once daily
3. **netilmicin** (*Netromycin*) iv,im, infusion 4-6mg/kg/day slow over 5min,
4. **Neomycin** sulphate po 1g/hr x 4hrs then 1g every 4hrs x 3days for gut sterilization and hepatic coma or topical ointment for skin abrasions.
5. **Tobramycin** 40mg/ml nebulized or iv,i.m 3-5 mg /kg/day in divided doses 8hrly neonates 2mg/kg/day bd.
6. **streptomycin** and **kanamyci**n ;see anti TB ,
7. **spectinomycin; im**

**MOA;** inhibit bacterial protein synthesis at 30s ribosomal sub unit /bactericidal

**Pharmacokinetics** most are administered IV, IM because of poor absorption from GI, t1/2=2-5hrs.

The blood plasma drug concentrations achieved during multiple daily dose therapy.

**NB; Single daily doses** Are at least as effective as and no more toxic than multiple daily doses.

It’s less nephrotoxic and ototoxic than more frequent dosing.

Since aminoglycoside uptake across the brush border of proximal renal cortical tubular cells is saturable, giving a single large dose should result in less renal accumulation.

Daily dosing with amikacin 🡪higher drug concentrations in bronchial secretions of patients with pneumonia.

Both the rate and extent of GIT absorption these are low. e.g more than 95% of an oral dose of neomycin is excreted unchanged in the feces.

The systemic bioavailability is low across other membranes. e.g gentamicin is poorly absorbed from a topical ophthalmic preparation, little bioavailability for inhaled tobramycin or instilled into the urinary bladder. Neomycin across intact skin is also low but absorption on damaged skin can be significant🡪nephrotoxicity can occur in burn patients.

They have aqueous solubility and modest binding to plasma and tissue proteins, their distribution corresponds to that of the extracellular fluid.

The central compartment corresponds to the intravascular space; the rapidly equilibrating compartment corresponds to the extracellular visceral space; the slowly equilibrating compartment largely corresponds to that of skeletal muscle; and the extremely slowly equilibrating compartment corresponds to that of bone, proximal renal tubules, otolymph, and other tissue where binding to phospholipids or mineral matrix occurs.

Gentamicin fails to reach intraocular fluid or CSF in significant concentrations after iv inj. although it reach bactericidal levels in CSF in patients with meningeal inflammation like meningitis.

Direct intrathecal injection of gentamicin may still be required for reliable bactericidal levels.

Nearly all of iV dose is cleared by the kidneys and can be recovered in the urine🡪 use in UTI. Elimination via GFR in urine. Needs dose adjustments in renal failure patients.

**MECHANISM OF ANTIBACTERIAL RESISTANCE OF AMINOGLYCOSIDES**

* Occur in aerobic gram-neg bacteria, plasmid-mediated expression of Ring one enzymes that acetylate, adenylate, or phosphorylate the aminoglycosides.
* Aerobic gram- ve bacilli to streptomycin are due to mutations in the proteins of the bacterial ribosomes.
* Streptococci, staphylococci, and Pseudomonadaceae resist drugs due to decreased transport of the aminoglycosides into the bacterial cytosol.
* Anaerobes resist them due to decreased transport into the bacterial cytosol.

Combining them with an antibiotic that disrupts the bacterial cell wall can overcome this natural resistance.

**Clinical uses**

Serious gram-negative bacillary infections

* Gentamicin is treat serious infections due to gram negative aerobic bacilli, such as escherichia coli and klebsiella pneumoniae, and proteus, serratia, acinetobacter, citrobacter, and enterobacter spp. gentamicin also has significant activity against staphylococcus aureus.
* They are combined with beta- lactams in the initial empirical therapy of sepsis.
* Gram-negative bacillary pneumonia.
* Acute salpingitis (pelvic inflammatory disease) due to *Neisseria gonorrhoeae, Chlamydia trachomatis,* or both is often complicated by superinfection with gram-negative bacilli and anaerobes.
* The combination with clindamycin in mx. an intraabdominal infection or an abscess secondary to penetrating trauma, diverticulitis, cholangitis, appendicitis, peritonitis, or postsurgical wound infection.
* Eradication of Facultative Gut Flora using **neomycin** and non absorbable erythromycin base given orally prior to colorectal surgery
* Topical neomycin plus bactricin applied as an ointment to prevent any infection of minor skin abrasions, burns, and cuts.
* Cystic Fibrosis--P. aeruginosa is commonly found in the bronchial secretions of patients with the disease. e.g daily inhalation of large doses of t**obr**amycin decreased the colonization these organisms
* Endocarditis; gentamicin and ampicillin is recommended as prophylaxis prior to surgery or instrumentation of the GIT or GUT for patients at high risk for endocarditis.
* Gentamicin or streptomycin will act synergistically with penicillin for the treatment of enterococci endocarditis.
* Meningitis; with the beta lactams or other antibiotics they penetrate CSF and the meninges.
* TB –MX. Streptomycin is useful in the initial therapy of severe or disseminated tuberculosis, which is most common in immunocompromised patients.
* kanamycin for 2nd line TB
* Ophthalmological mx. Infection due to high concentrations of gentamicin achieved in the conjunctival sac. treating bacterial ophthalmic keratitis.
* spectinomycin is used in gonococcal pharyngitis or systemic gonococcal urethritis
* streptomycin is used as an adjunct to doxycycline in brucellosis mx.

**Toxicity**

Nephrotoxic

Ototoxic 8th cranial nerve injury due to accumulation in otolymph esp streptomycin in infants or 2nd and 3rd trimesters of pregnancy.

Neurotoxic 🡺Aminoglycosides can cause neuromuscular junction blockade by displacing Ca ++from the neuromuscular junction, inhibiting the Ca++-dependent prejunctional release of acetylcholine and blocking postsynaptic acetylcholine receptor binding. worse in myasthenia gravis patients. Antidote iv ca++

other side effects; Nausea , skin reactions (very common in children) and vomiting

rarely; Anaemia, eosinophilia, fever, headache, hypomagnesaemia, paraesthesia, renal impairment, Bronchospasm , confusion and lethargy

**DRUG INTERUCTIONS**

* They worsens nephrotoxicity is additive with vancomycin, polymixin, gallium, furosemide, enflurane, cisplatin, and cephalosporins.
* Aminoglycoside nephrotoxicity is synergistic with that of amphotericin B and cyclosporine.
* Verapamil and Ca++ can lessen the nephrotoxicity, but the latter may inhibit the antibacterial effect

**gentamycin iv im slow iv or infusion 3mg-7.5mg/kg/day**

**INDICATIONS AND DOSE**

* Gram-positive bacterial endocarditis (in combination with other antibacterials)
* Septicaemia , Meningitis and other CNS infections ,Biliary tract infection ,Acute pyelonephritis Endocarditis ,Pneumonia in hospital patients , Adjunct in listerial, meningitis, Prostatitis
* CNS infections (administered on expert advice) intrathecal Adult: 1 mg-5mg daily.
* Surgical prophylaxis slow iv Adult: 1.5 mg/kg, to be administered over at least 3 minutes, administer dose up to 30 minutes before the procedure,
* Surgical prophylaxis in joint replacement surgery

**SIDE-EFFECTS**;

Antibiotic associated colitis . blood disorder, depression . encephalopathy . hallucination . hepatic reaction . neurotoxicity . peripheral neuropathy . purpura . seizure . stomatitis . vestibular damage

**Tobramycin** iv, slow iv, infusion, inhalation

**INDICATIONS AND DOSE**

* Septicaemia, Meningitis and other CNS infections , Biliary tract infection, Acute pyelonephritis or prostatitis , Pneumonia in hospital patients Adult: 3 mg/kg daily in 3 divided doses; increased if necessary up to 5 mg/kg daily in 3–4 divided doses,
* Urinary-tract infection **i.m** Adult: 2–3 mg/kg for 1 dose
* Chronic Pseudomonas aeruginosa infection in patients with cystic fibrosis; by inhalation of nebulised solution Adult: 300 mg every 12 hours for 28 days, subsequent courses repeated after 28-day interval without tobramycin nebuliser solution
* by inhalation of powder ;Adult: 112 mg every 12 hours for 28 days, subsequent courses repeated after 28-day interval without tobramycin inhalation powder

**Neomycin sulfate po**

**indications and dose**

Bowel sterilisation before surgery; Adult: 1 g /1 hr for 4 hrs, then 1 g / 4 hrs for 2–3 days

Hepatic coma ; po Adult: Up to 4 g daily in divided doses usually for 5–7 days

CONTRA-I;

Intestinal obstruction, myasthenia gravis (aminoglycosides may impair neuromuscular transmission)

**Chloramphenicol (Chloromycetin) po,iv,i.m (2hr)**

 It is a Nitrobenzene derivative, affects protein synthesis by binding to the 50S ribosomal subunit and preventing peptide bond formation

It prevents the attachment of the amino acid end of aminoacyl-tRNA to the A site.

**Antibacterial Spectrum**

A broad-spectrum antibiotic; effective against gram-positive and gram-negative bacteria, including Rickettsia, Mycoplasma, and Chlamydia spp., Haemophilus infuenza

Effective against anaerobic bacteria, including Bacteroides fragilis.

**PK.**

Rapidly and completely absorbed from GIT and not affected by food ingestion or metal ions.

Bind to serum albumin, penetrates the brain and CSF and crosses the placental barrier.

Inactivated in the liver by glucurononyl transferase. Metabolism is by hepatic, rapidly excreted (80–90%) in the urine.

Renal elimination is by tubular secretion and glomerular filtration.

**The PO dose** 500mg or 50-100mg/kg/day in 4 divided doses or 6 hourly. Serious infections given IV.

**Clinical uses**

* Treatment of specific bacterial causes of meningitis: Haemophilus influenzae, Neisseria meningitidis, and S. pneumoniae.
* Effective against H. influenzae–related arthritis, typhoid and paratyphoid fever, osteomyelitis, and epiglottitis.
* Topical treatment of eye infections.
* Cerebral abscesses caused by anaerobic bacteria that are resistant to penicillins.

**ADR**

**Gray baby syndrome in neonates**. This syndrome is characterized by abdominal distention, vomiting, progressive cyanosis, irregular respiration, hypothermia, and vasomotor collapse. This is due to inability to conjugate by the liver glucoronyl.

**Toxic bone marrow** depression or idiosyncratic aplastic anemia.

O**thers**; nocturnal hemoglobinuria, neuritis, urticarial

**Lincosamides**; =**Clindamycin**

**Mechanism of Action**

They include lincomycin (Lincocin) and clindamycin (Cleocin)

They inhibit protein synthesis. They bind to the **50S** ribosomal subunit at a binding site overlapping the binding sites for chloramphenicol and erythromycin.

They block peptide bond formation by interference at either the A or P site on the ribosome.

**pk -**the absorption **is not affected by food in the gut** for clindamycin and lincomycin.

Peak serumlevels can be obtained 1 hour after i.v administrationof clindamycinand approximately 90% of theantibiotic is protein bound. Both are metabolized by the liver, and 90% of the inactivated drug is excreted in the urine.

They penetrate most tissues well, including bone. **Don’t** readily penetrate the normal or inflamed meninges. They readily pass through the placental barrier. Their t1/2= 2 -2.5 hrs.

**Dose**

Oral: 300–600 mg every 6 hrs in adults. I.v: 2.4 g clindamycin daily is given in 4 divided doses by slow intravenous infusion in adults. child 15-40mg/kg/daily in 4 divided doses.

**Clinical Uses**

* Clindamycin is highly active against staphylococci bone/joint infections and streptococci other than enterococci,*S. pyogenes* (group A strep).
* Peritonitis, endocarditis prophylaxis
* Topically against *Corynebacterium acnes* in patients who cannot tolerate tetracyclines.
* Active against anaerobic bacteria

**Adverse Effects**

* Hypersensitivity rashes/ Steven Johnson syndrome and diarrhea. The rash is usually itchy, morbilliform generalised.
* Gastrointestinal intolerance with abdominal pain, nausea, and vomiting occurs infrequently. G.I. Irritation and pseudomembranous colitis.
* abscess at injection site i.m, thrombophlebitis
* Hepatotoxicity
* Bone marrow suppression 🡪thrombocytopenia.

**SODIUM FUSIDATE (tabs, iv infusion)**

**Uses**

**Fusidic acid** is combined with other drugs to treat staphylococcal infections, including **penicillin**-resistant strains. It penetrates tissues (including bone, endocardium) well.

 It is normally used in conjunction with **flucloxacillin** for serious staphylococcal infections.

It is also available as eye drops for the treatment of bacterial conjunctivitis.

**MOA**

It inhibits bacterial protein synthesis.

**dosage;** iv infusion 6mg-7mg/kg tds max 500mg vial

Tabs 50mg/kg in three divided doses . max 750mg

**Adverse effects**

Adverse effects are rare, but include reversible cholestatic jaundice.

**Pharmacokinetics**

When administered either orally or iv, its t1/2-4-6 hours and it is excreted primarily via the liver.

**Oxazolidinone**

**MOA**

Inhibits formation of the 70S ribosomal initiation complex, preventing bacterial protein synthesis; primarily bacteriostatic action.

**Spectrum of activity.** Gram-positive bacteria and a few Gram-negative anaerobic bacteria staphylococci, pneumococi, enterococci, plus those resistant to penicillin and vancomycin.

|  |  |  |  |
| --- | --- | --- | --- |
| **Week 6:** |  |  | Drugs that inhibit protein synthesis – macrolides, tetracyclines. |

**Macrolide antibiotics** (2hr)

**Examples;** erythromycin (*Ilotycin, E-mycin, Robimycin*), clarithromycin (Biaxin), azithromycin (*Zithromax)*, Spiramycin and oleandomycin (*Matromycin*) *, trolendromycin*

The Structure- Consists of a large lactone ring to which sugars are attached.

**Mechanism of Action**

bacteriostatic

Macrolides bind to the **50**S ribosomal subunit of bacteria thus inhibiting of translocation

**Antibacterial Spectrum**

The macrolides are effective against a number of organisms, including Mycoplasma spp., H. influenzae, Streptococcus spp. (including S. pyogenes and S. pneumoniae), staphylococci, gonococci, Legionella pneumophila, and other Legionella spp.

Clarithromycin and azithromycin have significant activity against Mycobacterium avium complex.

**P.K** -absorbed from the intestinal tract, although the presence of food interferes with absorption and part of the dose is destroyed acid lability of these antimicrobials. It’s coated for good absorption., diffuse readily into tissues and cross placental membranes and CSF. **Excreted** -primarily in active form in bile less in urine.

The half-life of erythromycin= t1/2 1-4 hrs, clarithromycin t1/2=3 - 7hrs and azithromycin t1/2= 68 hrs.

**Clinical Uses**

* Treatment of Mycoplasma pneumoniae infections,
* **eradication** of Corynebacteriumdiphtheriae from pharyngeal carriers and preparoxysmal stage of pertussis erythromycin 500 mg qid x7-10days.
* chlamydial infection
* Chronic prostatitis
* The treatment of Legionnaires’ disease,
* Campylobacter enteritis
* Prevention of pneumococcal infection in asplenia or in SCD (if penicillin-allergic)
* Chlamydial conjunctivitis
* Prevention of recurrence of rheumatic fever/erythromycin
* skin infections.
* Prevention of secondary pneumonia in neonates.
* Erythromycin ->treatment and prevention of S. pyogenes and other streptococcal
* Clarithromycin has activity against Toxoplasma gondii and Mycobacterium avium intracellular infections.
* erythromycin is 2nd -line drug for the treatment of gonorrhea and syphilis.
* Although erythromycin is popular for the treatment of middle ear and sinus infections, including H. influenzae, possible erythromycin-resistant S. pneumoniae.
* treatment of STI with azithromycin due protein binding and to long t1/2
* Clarithromycin is also used in regimens for Helicobacter pylori eradication.
* Spiramycin is also a macrolide which is used for the treatment of toxoplasmosis.
* Clarithromycin has activity against Toxoplasma gondii and Mycobacterium avium intracellular infections.

N/B; Azithromycin has less coverage against these organisms, and because of its lower peak serum concentrations and prolonged protein binding, it partitions less well across bronchial membranes.

**Side effects**

* Mild GIT upset with nausea, diarrhea, and abdominal pain
* taste altered
* Hypersensitivity reaction that includes fever and eosinophilia.
* Thrombophlebitis on IV
* Transient impairment of hearing.
* Cholestatic hepatitis 🡪jaundice may occur when taken > 10 days
* rarely pancreatitis
* sensation abnormal .
* skin reactions .
* sleep disorders
* vasodilation
* Chest pain and cardiac arrhythmias.

**Caution**; breast feeding, pregnancy, liver impairement, neonates<2wks🡪 hypertrophic pyloric stenosis due to colitis.

**Drug interaction with macrolides;** induce hepatic microsomal enzymes and interfere with the actions of various drugs, including theophylline and carbamazepine,digoxin, anticoagulants.

 **Dose**

**Erythromycin iv 1g, po 250mg, 500mg**

Oral: 250–500 mg 6-hourly for adults /12.5-25mg/kg. I.v: 500 mg–1 g by infusion 6-hourly for adults. 25-50mg/kg for children.

syphilis po; Adult: 500 mg 4 times a day for 14 days

**Clarithromycin**:po250mg, 500mg

po: 500 mg 12-hourly for adults. I.v: 500 mg 12-hourly. severe infections for 14days.

Helicobacter pylori eradication in combination with PPIand amoxicillin po: 500 mg twice daily

H- pylori eradication in combination with a PPI and metronidazole po: 250 mg twice daily

**Azithromycin po250mg, 500mg, susp, iv infusion 500mg**:

For non-gonococcal urethritis/ cervicitis 1g stat or 10mg/kg/day for 3 days.

For prophylaxis of strep infection; 12 mg/kg once daily (max. per dose 500 mg) for 5 days

**Tetracycline s**

**Examples**

Minocycline =t1/2=16hrs

doxycycline =t1/2=18hrs

Oxytetracycline =t1/2=9hrs

tetracycline =t1/2=8hrs

Troleandomycin t=1/2=9hrs

**MOA**

Their primary mode of action is inhibition of protein synthesis.

Binds to the 30S ribosome and thereby prevent the binding of aminoacyl transfer

RNA (tRNA) to the A site.

They are broad-spectrum, effective against both gram-positive and gram-negative bacteria, including Rickettsia, Coxiella, Mycoplasma, and Chlamydia spp.

**P.K**

Absorption of doxycycline and minocycline is improved with food.

Doxycycline is given once daily and its not contraindicated in renal impairment.

tetracycline form insoluble chelates with calcium (found in many antacids), magnesium, and other metal ions, their administration with milk (calcium), magnesium hydroxide, aluminum hydroxide, or iron interferes with absorption metabolism in the liver and are concentrated in the bile.**Excretion** ; in faeces mostly then urine.

**Drug interactions**

Tetracyclines chelate calcium and iron in the stomach, and their absorption is reduced by the presence of antacids or food.

**Uses/indications**

* Doxycycline is a potential first-line in the prophylaxis of anthrax after exposure
* Minocycline is an effective alternative to rifampin for eradication of meningococci
* The tetracyclines are still the drugs of choice for treatment of cholera, diseases caused by Rickettsia and Coxiella, granuloma inguinale, relapsing fever, the chlamydial diseases (trachoma, lymphogranuloma, non-specific urethritis. 500mg qid x7days -14days
* The treatment of brucellosis, and infections caused by Pasteurella and Mycoplasma spp.
* Tetracyclines are clinically effective in acne***dose*** *;12-adults 250-500mg bd x 3months*

**Adverse Effects**

* Oral administration can cause nausea, vomiting, epigastric burning, stomatitis, and glossitis, and an i.v injection can cause phlebitis.
* When given over long periods use🡪 negative nitrogen balance leading to elevated blood urea nitrogen.
* Hepatotoxicity occurs infrequently but is particularly severe during pregnancy,
* in uremia and increasing jaundice can be fatal/hyperbilirubinemia.
* pancreatitis .
* hypersensitivity reactions (including rash, exfoliative dermatitis, Stevens–Johnson syndrome, urticaria, angioedema, anaphylaxis, pericarditis)
* nephrotoxic
* Staining of both the deciduous and permanent teeth and retardation of bone growth can occur if tetracycline’s are administered after the fourth month of gestation or if they are given to children < 8 years of age.
* Superinfection may result in oral, anogenital, and intestinal Candida albicans infections, Staphylococcus aureus or Clostridium difficile overgrowth may cause enterocolitis and fungal esophagitis

**Indications**

**Doxycycline po 100mg**

* Susceptible infections (e.g. chlamydia, rickettsia and mycoplasma)
* Acute sinusitis
* Severe infections (including refractory urinary-tract infections)
* Acne
* Rosacea/Papulopustular facial rosacea (without ocular involvement)
* Early syphilis Adult: 100 mg twice daily for 14 days
* Late latent syphilis Adult: 100 mg twice daily for 28 days
* Neurosyphilis Adult: 200 mg twice daily for 28 days
* Uncomplicated genital chlamydia , Non-gonococcal urethritis;Adult: 100 mg twice for 7 days
* Pelvic inflammatory disease; Adult: 100 mg twice daily for 14 days
* Lyme disease (under expert supervision) Adult: 100 mg twice daily for 10–14 days (for 28 days in Lyme arthritis)
* Anthrax (treatment or post-exposure prophylaxis) Adult: 100 mg twice daily
* Prophylaxis of malaria ; 100 mg once daily, to be started 1–2 days before entering endemic area and continued for 4 weeks after leaving, can be used for up to 2 years
* Adjunct to quinine in treatment of P.falciparum malaria Adult: 200 mg daily 7 days
* Periodontitis (as an adjunct to gingival scaling and root planning); Adult: 200 mg twice daily for 3 months.
* The treatment of brucellosis, and infections caused by Pasteurella and Mycoplasma spp.
* **Minocycline** ; effective alternative to rifampin for eradication of meningococci

**The tetracyclines** are still the drugs of choice for treatment of cholera, diseases caused by Rickettsia and Coxiella, granuloma inguinale, relapsing fever, the chlamydial diseases (trachoma, lymphogranuloma, non-specific urethritis, acne.

|  |  |  |  |
| --- | --- | --- | --- |
| **Week 7:** |  |  | Antimycobacterial drugs – anti-tubercular drugs, treatment of tuberculosis. |

**Antituberculous drugs**

* Mycobacterium tuberculosis multiplies slowly and the long periods of treatment required encourage the emergence of resistant strains.
* Combination chemotherapy is thus the basis of treatment.
* Because of increasing drug resistance (usually as a consequence of poor adherence),
* antituberculosis drugs that are classified as first-line drugs are superior in efficacy and possess an acceptable degree of toxicity.
* The initial treatment is with four drugs: **isoniazid, rifampicin, ethambutol** and **pyrazinamide**, administered for 2months.
* Fixed dose combinations or Co-formulation of rifampicin, isoniazid and pyrazinamide allows for simplification of therapy.
* Subsequently,**4** months **isoniazid and rifampicin** are given (again usually co-formulated), as long as cultures indicate that the organism is susceptible.
* **Six** months of treatment with this regimen is adequate pulmonary TB.
* Longer period of therapy is necessary in CNS TB and in selected other extra-pulmonary cases.
* In patients at risk of poor adherence ‘directly observed therapy **dot** on a two weekly basis is preferred.

**The objectives of tuberculosis therapy are:**

1. To reduce the bacillary population rapidly thereby decreasing severity of the disease, preventing death and halting transmission of M. tuberculosis;
2. To eradicate persisting bacilli in order to achieve durable cure (prevent relapse) after completion of therapy
3. To prevent acquisition of drug resistance during therapy.

**The three basic concepts in tuberculosis treatment are as follows:**

Regimens must contain multiple drugs to which the organism is susceptible.

Drugs must be taken regularly.

Drug therapy must continue for a sufficient time.

**The following dosages of first-line anti-TB medicines should be used daily for the treatment of TB:** **As children approach a body weight of 25 kg, adult dose can be used.**

|  |  |
| --- | --- |
|  Isoniazid (H)  | 10 mg/kg (range 7–15 mg/kg) max 300 mg |
| Rifampicin (R)  | 15 mg/kg (range 10–20 mg/kg) max300mg |
| Pyrazinamide (Z)  | 35 mg/kg (range 30–40 mg/kg)  |
| Ethambutol (E)  | 20 mg/kg (range 15–25 mg/kg) 400 mg |

**PULMONARY TB treated for 6 months**

**abdominal TB, TB adenitis treated for 6** *months*

* Fixed dose combination tablets available for adults and children >8yrs/ >30kg

**Intensive Phase**; 2RHZE (150,75,400, 275mg) and **Continuation Phase**; 4RH (150,75mg)RH (300,150mg)

* Children dispersible tablets are available

**Intensive Phase**; 2RHZE (75mg,50mg,150mg, 100mg) and **Continuation Phase**; 4RH (75mg,50mg) N/B ethambutol is separate in paediatrics formulation as a single dose of 20mg/kg /day. Max 25mg/kg.

**EXTRA PULMONARY TB treated for 12months for ( TBM, TB spine, TB bone)**

Intensive Phase; **2RHZE (150,75, 400, 275mg**)

Continuation Phase; **10 RH (150,75mg)RH (300,150mg)**

**N/B** add a steroid to avoid adhesions

1. **Isoniazid or INH iv 25mg/ml, tabs 50mg**

**MOA**

Isoniazid is a synthetic agent with a structural similarity to that of pyridoxine.

Inhibits a step in the biosynthesis of essential fatty acids within mycobacteria. Isoniazid (isonicotinic acid hydrazide, or INH) 🡪the most active drug for the treatment of TB caused by susceptible strains. Active against susceptible bacteria only when undergoing cell division. Bactericidal against actively growing *M. tuberculosis* and bacteriostatic against non-replicating organisms.

**Pk;** Isoniazid does not bind to serum proteins; it diffuses readily into all body fluids and cells, including the caseous TB lesions. Isoniazid is well absorbed following oral administration and is distributed throughout the body, including the CSF where concentrations equal those in blood. Isoniazid is inactivated in the liver by pathways/ acetylation. The same metabolic pathway is involved in the acetylation of hydralazine, procainamide and dapsone. Rapid acetylators are more prone to hepatotoxicity. Slow acetylators tend to develop peripheral neuropathy more readily.

**Clinical Uses;**

The safest and most active mycobactericidal agent.

used in all therapeutic and prophylactic regimens for susceptible tuberculosis infections.

The same dosage is recommended as preventive therapy over **six** months for children under the age of 5yrs as well as HIV-positive children of any age.

The first-line drug combinations for use in all types of tuberculous infections.

It’s preferred as a single agent in the treatment of latent TB infections in high-risk persons with positive tuberculin skin reaction with no radiological or other clinical evidence of TB.

**Adverse effects;**

Peripheral neuropathy in slow acetylators and can be prevented by co-administration of pyridoxine (20 mg/day), In 10-20% patients.

risk of neurotoxicity; compared with fast acetylators, it is more frequent in slow acetylators because slow acetylators achieve higher drug plasma levels. Isoniazid promotes renal excretion of pyridoxine, resulting in a relative deficiency and neuropathy.

CNS toxicity may range from excitability and seizures to psychosis.

Hepatotoxicity and frequent in the elderly and those with a large alcohol intake. other risk factors for hepatitis include underlying liver disease, pregnancy, and combination therapy with acetaminophen.

Very high doses lead to psychosis, convulsions or coma.

gastrointestinal (GI) intolerance, anemia, rash, tinnitus, and urinary retention

**Drug interactions**

Isoniazid inhibits enzymes that metabolize phenytoin and warfarin; thus, phenytoin concentrations and anticoagulation level should be carefully monitored. 🡪to potentiation effect with these drugs.

**Dose INH(PO,IV)**

Oral: 5 -10mg/kg daily in children, i.e. children require more on a weight basis; for tuberculous meningitis, 10 mg/kg daily. Also available for parenteral use.

1. **Rifampicin, tabs 150,300mg**

**MOA**

It is bactericidal.

Binds strongly to the β-subunit of bacterial DNA inhibiting the DNA-dependent RNA polymerase of Mycobacterium sp. Rifampin does not affect mammalian polymerases.

Rifampin is a semisynthetic macrocyclic antibiotic produced from *Streptomyces mediterranei.*

It is a large lipid-soluble molecule

It is Bactericidal for both intracellular and extracellular microorganisms.

**Pk**- well absorbed following oral administration and widely distributed plus CSF. Absorption is impaired if rifampin is given concurrently with aminosalicylic acid or is taken immediately after a meal, 60-90% protein bound. It is deacetylated in the liver and 65%eliminated by biliary excretion in feces. It can induce its metabolites.

Peak concentration 4hrs**.**

**Antibacterial Activity and Resistance**

M. tuberculosis, rifampin is active against Staphylococcus aureus, Neisseria meningitidis, brucella, Haemophilus influenzae, Chlamydiae, and certain viruses. Rifampin resistance results from a point mutation or deletion in rpoB, the gene preventing its binding of RNA polymerase

**Adverse effects**

* There is transient elevation of liver enzymes but serious hepatotoxicity is uncommon.
* The risk of liver damage is increased by alcoholism and pre-existing liver disease.
* Hepatotoxicity is uncommon but occurs in alcoholism and pre-existing liver disease.
* Intermittent treatment is associated with more frequent and serious advers effects, including renal failure and thrombocytopaenia.
* Red urine, tears and sputum

There is often a transient elevation of liver enzymes cytochrome p- 450 leading to increased metabolism of many drugs this complicates the treatment of TB in HIV-infected patients whose regimen includes protease inhibitors and non-nucleoside reverse transcriptase.

Ri**fabutin** has relatively little of these effects now commonly substituted for rifampin in the treatment of tuberculosis in HIV-infected patients.

**Clinical Uses**

* Rifampin is a first-line anti-TB drug for pulmonary and extra-pulmonary TB.
* Rifampin is an alternative to isoniazid in the treatment of latent tuberculosis infection.
* May be combined with an antileprosy agent for the treatment of leprosy.
* Protects those in close contact with patients having H. influenza type b and N. meningitidis infection.
* Used in methicillin-resistant staphylococcal infections, such as osteomyelitis and prosthetic valve endocarditis.

**Drug interactions**

Rifampicin induces hepatic enzymes and hence, because of increased clearance, can cause treatment failure with oral contraceptives, sulphonylureas, warfarin, steroids and barbiturates. There are significant drug interactions with many antiretroviral agents e.g NVP.

**Dose;**

Rifampicin is given at a dose of 10 mg/kg daily one to 2 hours before breakfast.

An intravenous formulation is also available.

1. **Ethambutol tabs 100mg**

**MOA;**Ethambutol is a water-soluble, heat-stable compound that inhibits arabinosyl transferase enzymes that are involved in bacterial cell wall biosynthesis. its bacteriostatic. Active against strains of M. tuberculosis and M. kansasii and Mycobacterium avium.

Drug resistance relates to point mutations in the gene (EmbB) that encodes the arabinosyl transferases that are involved in mycobacterial cell wall synthesis.

**PK;** Ethambutol is well absorbed following oral administration.

It has poor penetration of CSF but otherwise is adequately distributed. Excretion of unchanged drug is mainly renal.

**Adverse effects;** most important reaction retrobulbar neuritis🡪loss of visual accuity and colour vision. **can be** preventable by using doses below 25 mg/kg daily.

The visual defect usually reverses over several months after stopping the drug.

**Drug Drug interactions**

Aluminium hydroxide can decrease absorption.

Dose- A daily dose of 15 mg/kg is given.

1. **Pyrazinamide ;tabs 500mg**

**MOA;** Pyrazinamide is a synthetic analogue of nicotinamide.

Bactericidal and component of intensive 2-month phase in short course (6 months) anti-TB therapy.

Its exact mechanism of action is on mycobacterial fatty acid synthetase involved in mycolic acid biosynthesis.

**PK;** It is well absorbed following oral administration and has good penetration to CSF. It is eliminated by renal excretion. Plasma t1/2= 9 -10 hours in patients with normal renal function.

**Adverse effects;** Pyrazinamide causes hepatotoxicity and arthralgia.

Dose modification is required in patients with renal impairment.

Inhibit excretion of urates🡪hyperuricemia and Gout (rare).

others; Rash, GI upset, Joint aches.

 n/b Pyrazinamide is not recommended for use during pregnancy.

**Dose;** A daily dose of 1.5 g (\_50 kg) to 2 g (\_50 kg).

1. **Rifabutin; caps 150mg**

Rifabutin (*Mycobutin*), an antibiotic related to rifampin, shares its mechanism of action, that is, inhibition of RNA polymerase. Has activity in vitro and in vivo against *M. avium-intracellular* and *M. tuberculosis,* including some rifampin resistant strains, such as *M.leprae* and *M.fortuitum.*

It has cross-resistance with rifampicin.

**pk**; Rifabutin is well absorbed orally, and peak plasma concentrations are reached in 2 -3 hours. Because of its lipophilicity, rifabutin achieves a 5- to 10-fold higher concentration in tissues than in plasma. Has a half-life range of 16 to 96 hours.

Elimination; urine and bile.

Rifabutin is as effective as rifampin in the treatment of drug-susceptible tuberculosis and is used in the treatment of latent TB infection either alone or in combination with pyrazinamide.

**Clinical use;** It is a less potent inducer of cytochrome 450 enzymes than Rifampicin thus less drug interaction with the protease inhibitors and non-nucleoside reverse transcriptase inhibitors, thus substituted for rifampin in the treatment of TB in HIV-infected patients.

It prevents *M. avium-intracellular* complex (MAC) isolates from both HIV-infected and non–HIV-infected individuals.

**dose** of rifabutin TB 150mg-450mg od for 6months

prophylaxis 300mg od for avium

**Summary of Common anti TB side effects Drug(s) responsible**

**Minor**

Anorexia, nausea, abdominal pains -🡪Rifampicin

Joint pains -------------------------------🡪Pyrazinamide

Burning sensation in feet---------------🡪Isoniazid

Orange/ red coloured urine -----------🡪Rifampicin

**Major**

Skin itching/ rash--------------------------🡪 Streptomycin, Rifampicin, Isonazid

Deafness (no wax on otoscopy)--------🡪 Streptomycin

Dizziness (vertigo, nystagmus) ---------🡪Streptomycin

Jaundice (other causes excluded)------🡪Isoniazid, Rifampicin, Pyrazinamide

Vomiting, confusion-----------------------🡪 Isoniazid, Rifampicin, Pyrazinamide

Visual impairment/ loss ------------------🡪Ethambutol

Generalised purpura, shock and purpura🡪 Rifampicin

**SECOND-LINE DRUGS/for MDR (18 months)- Resistance to rifampicin or isoniazid**

**N/B**; do gene xpert sputum, gastric lavage or nasopharyngeal aspirate for children to test resistance to both **isoniazid** and **rifampicin**

1. **Streptomycin** is now infrequently used.

It is an aminoglycoside that is eliminated by the kidneys.

Ototoxicity is the main adverse reaction. Streptomycin could particularly be considered for use in patients with liver disease.

Several other agents are available for use in situations of bacterial resistance or adverse reactions to first-line drugs, e.g. capreomycin, cycloserine, prothionamide,-aminosalicylic acid, amikacin, thiacatezone and linezolid.

**MDR ;** Multi-drug resistant TB is defined as resistance to both **isoniazid** and **rifampicin**. Treatment is usually with as many susceptible agents as tolerated for at least **18 months.**

1. **Cycloserine;** po

**MOA**

It is structural analogue of D-alanine and acts through a competitive inhibition of the D-alanine that is involved in bacterial cell wall synthesis. discovered from Streptomyces orchidaceus.

**PK**; given po ,bioavailability 70-90 %,metabolism in the liver , elimination t1,2 10hrs in normal kidney. excreted in kidney.

**spectrum of activity**

A broad-spectrum antibiotic

Inhibits M. tuberculosis and active against E, coli, S. aureus, and Enterococcus, Nocardia, and Chlamydia spp. It is used in the treatment of MDR tuberculosis and is useful in renal tuberculosis since most of the drug is excreted unchanged in the urine.

other uses; psychiatry in anxiety disorders.

**dose**; Capsule (250 mg) Adults 10–15 mg/kg total (usually 250–500 mg once or twice daily).Children 15–20 mg/kg daily.

**SE;** CNS; headache, vertigo , drowsiness, tremor ,convulsios, and psychosis. megaloblastic anaemia.

1. **Tabs prothionamide(** pto) or ethionamide po 15-20mg/kg/day adults 500mg ( max 1g)

**MOA;** bacteriostatic or bactericidal. inhibits bacteria cell wall synthesis (mycolic acid/long fatty chain in mycobacteria cell wall as isoniazid. effective in treatment of mdr tb .

PK; well absorbed po with or without food but administered with food,crosses BBB to achieve concentration in the CSF as the plasma.

**S.E**; n/v, depression, hallucinations; jaundice, peripheral neuropathy give with pyridoxine. hypothyroidism as it inhibits thyroid hormone synthesis as methimazole.

**c/I;** pregnancy teratogenic, liver disease

1. **Amikacin/ kanamycin**;

Aqueous solution (500 mg and 1 g vials) for IM or IV administration. Adults 15 mg/kg daily Children 15–20 mg/kg.

1. **Capreomycin;IV ,** **deep I,M**

grouped under aminoglycosides, produced from streptomyces

Aqueous solution (1 g vials) for deep IM or IV; Adults 15 mg/kg daily. Children 15–20 mg/kg.

Poorly absorbed from GI tract and so must be given parenterally.

Excreted mainly unchanged in the urine following glomerular filtration.

**Side effects;** hypersensitivity reactions like urticarial, leukocytosis, asthma like symptoms

changes in liver function tests,

vertigo, neuromuscular block, hearing loss.

hematuria increased urine output

poor appetite, N/V

ototoxicity/damage 8th cranial nerve

nephrotoxicity, hypokalemia

**DRUG inteructions**

Increased nephrotoxicity with Lasix, kanamycin, amphotericin b, vancomycin

Worsening ototoxicity and neuromuscular blockade with other aminoglycosides

With opioids 🡪increased respiratory inhibition or apnea

Antihistamines increases vertigo, tinnitus and ototoxicity

**c/I ;** pregnancy due to ototoxicity nephrotoxicity to the fetus.

1. **Para-amino salicylic acid (PAS);**

Granules (4 g packets) can be mixed in and ingested with soft food (granules should not be chewed). Tablets (500 mg) are still available in some countries, but not in the United States. Children 200–300 mg/kg.

**MOA;**It inhibits folic acid synthesis without potentiation with antifolic compounds,also inhibits mycobacteria cell wall (mycobactin) synthesis reducing iron uptake by the bacteria.

**Pk;** It penetrates tissues and reaches high concentrations in the TB cavities and caseous tissue. Peak plasma levels are reached within 1-2hrs of admin, and has a half-life of 1 Hr. metabolized by hepatic acetylation. When combined with isoniazid, PAS can function as an alternative substrate and block hepatic acetylation of isoniazid, thereby increasing free isoniazid levels.

**SE;** GIT ; abdominal pain,n/v/ d, hypersensitivity reaction e.g fever, skin rash exfoliative dermatitis, leucopenia, agranulocytosis, thrombocytopenia. positive coombs test, hemolytic anemia, jaundice , pericarditis, hypoglycemia, optic neuritis, encephalopathy. crystalluria rx maintain of urine ph neutral or alkaline

1. **Levofloxacin;** po,iv

Tablets (250 mg, 500 mg, 750 mg); aqueous solution (500 mg vials) for IV injection.

Adults 500–1000 mg daily. Children 15–20 mg/kg.

1. **Moxifloxacin;**

Tablets (400 mg); aqueous solution (400 mg/ 250 mL) for IV injection. Adults 400 mg daily. Children 10 mg/kg daily. They inhibit of bacterial DNA gyrase. Resistance is the result of spontaneous mutations in genes that either change the DNA gyrase or decrease the ability of the drug to cross the cell membrane.

N/B Levofloxacin and mefloxacin are used in place of Ethambutol during intensive phase in adults in whom it cannot be used, or in place of INH throughout treatment in adults in whom INH cannot be used.

1. **Beta Lactam and Clavulanate Antibiotics;**

All mycobacteria produce beta lactamase. In vitro, several beta lactamase-resistant antibiotics or amoxicillin clavulanic acid, are active against M. tuberculosis and non-TB mycobacteria.

1. **Clarithromycin with azithromycin**, given orally in combination with other drugs,

**Drug Interactions**

* Rifamycins (Rifambicin and least Rifabutin) on the metabolism of other drugs. They induce variety of metabolic pathways. (Induce cytochrome P450) metabolizes PIs and NNRTIs reducing their concentration.
* Enzyme inhibitors of CYP3A increase the serum concentrations of Rifabutin and one of its metabolites (25-O-desacetyl-rifabutin).
* Absorption of the fluoroquinolones is markedly decreased by ingestion of medications containing divalent cations (calcium, iron, zinc).

**MDR management of multidrug resistance TB minimum duration of treatment 18 months.**

|  |  |
| --- | --- |
| **Intensive phase** **6**(km,pto,Lfx,cs,E/Z) | **Continuation phase** upto **18m**(pto,lfx,cs E/Z) |
| Inj kanamycin (km) |  |
| Tabs prothionamide (pto) | Tabs prothionamide |
| Tabs levofloxacin(Lfx) | Tabs levofloxacin |
| Tabs cycloserine(Cs) | Tabs cycloserine |
| Tabs ethambutol (E)or tabs pyrazinamide (Z) | Tabs ethambutol or pyrazinamide |

**XDR-TB( poly-resistantTB or is resistance from the 2nd -line group (e.g. extensively drug-resistant TB);**

Resistance to **pyrazinamide** and **fluoroquinolone** or injectables aminoglycosides

For TB specialist refer management

proposed 3rd line; macrolides e.g clarythromycin, linezolids, thizetazones vitamin D, thioridazine

**Patients for DOT**

* have a history of non-adherence
* have previously been treated for tuberculosis
* are in denial of the tuberculosis diagnosis
* have MDR tuberculosis
* have a major psychiatric or cognitive disorder
* have a history of homelessness, drug or alcohol misuse
* are in prison, or have been in the past 5 years;
* are too ill to self-administer treatment;
* request directly observed therapy.

**clofazimine (lambrene) caps 50mg-100mg /day**

it’s a phenazine dye

**MOA**; inhibits mycobacteria DNA replication and cell growth.

Has anti mycobacterial and anti inflammatory activity.

**pk**; po biological t1/2 =70days , metabolized in the liver

its oral absorption is quite variable, with 9 to 70% of the drug eliminated in the feces.

It achieves significant concentrations in tissues, including the phagocytic cells; . It is primarily excreted in bile, with less than 1% excretion in urine.

**spectrum of activity** ; m avium in patients with HIV, m leprae , resistant MDR Tb

**SIDE EFFECTS**; abdominal pain, diarrhea, dry skin, pink to brownish skin and body fluids colour change but clears after 6-12 months after stoppage, depression, increased blood sugar, git lining swelling🡪 paralytic ileus, git bleeding, bowel obstruction, splenic infarction

|  |  |  |  |
| --- | --- | --- | --- |
| **Week 8:** |  |  | Antimycobacterial drugs – anti-leprosy drugs, treatment of leprosy. |

**Anti- leprosy**

Leprosy is a chronic infectious disease caused by Mycobacterium leprae.

Current recommendations for the treatment of leprosy suggest multidrug regimens rather than monotherapy because such a regimen has proven to be more effective, delays the emergence of resistance, prevents relapse, and shortens the duration of therapy.

**Three Drugs regimen for multibacillary leprosy**

1. **dapsone** 1-2mg/kg max 100mg/day <35kg = 50mg/day
2. **clofazimine,** 300mg monthly or 50mg daILY
3. and **rifampin. 600 Mg monthly OR < 35kg =450 Mg**

 **Two Drugs regimen for paucibacillary leprosy**

1. dapsone 1-2mg/kg max 100mg/day <35kg = 50mg/day
2. and rifampin. 600 Mg monthly OR < 35kg =450 Mg

Treatment of tuberculoid leprosy is continued for at least 1 -2 years, while patients with lepromatous leprosy are generally treated for 5 years.

 **Dapsone and Sulfones [po}**

The sulfones are structural analogues of P Dapsone (Avlosulfon). A long-term therapy of leprosy. Although the sulfones are highly effective against most strains of M. leprae some are less susceptible and can persist for many years, resulting in relapse.

**PK**; Sulfones, such as dapsone and sulfoxone (Diasone),

They are well absorbed orally and are widely distributed throughout body fluids and tissues.

Peak concentrations of dapsone are reached within 1 -3 hrs of oral administration

half-life of 21 - 44 hrs. 50% of dapsone is bound to serum proteins.

The sulfones tend to remain in the skin, muscle, kidney, and liver up to 3 weeks after therapy is stopped.

The concentration in inflamed skin is 10 - 15 times higher than that found in normal skin. They are retained in the circulation for a long time (12–35 days) because of hepatobiliary drug recirculation. They are acetylated in the liver, and 70 to 80% of drug is excreted in the urine as metabolites.

**use**

Dapsone, combined with rifampin and clofazimine in the treatment of both **multi-bacillary** and **pauci -bacillary M. leprae** infections.

PO Adult (body-weight up to 35 kg): 50 mg daily OR 1–2 mg/kg daily, may be selfadministered Adult (body-weight 35 kg and above): 100 mg daily, may be self-administered

Dermatitis herpetiformis

The treatment and prevention of Pneumocystis carinii pneumonia in AIDS patients who are allergic to or intolerant of trimethoprim– sulfamethoxazole (septrin). dose; 1-2mg/kg/day max 100mg/day.

**Side effects**

non-hemolytic anemia, methemoglobinemia, acute hemolytic anemia in persons with a G6PD deficiency, dermatitis. Rarely fever, pruritus, paresthesia, reversible neuropathy, and hepatotoxicity.

**clofazimine (lambrene) caps 50mg-100mg /day**

it’s a phenazine dye

**MOA**; inhibits mycobacteria DNA replication and cell growth.

Has anti mycobacterial and anti inflammatory activity.

**pk**; po biological t1/2 =70days , metabolized in the liver

its oral absorption is quite variable, with 9 to 70% of the drug eliminated in the feces.

It achieves significant concentrations in tissues, including the phagocytic cells; . It is primarily excreted in bile, with less than 1% excretion in urine.

**spectrum of activity** ; m avium in patients with HIV, m leprae , resistant MDR Tb

**SIDE EFFECTS**; abdominal pain, diarrhea, dry skin, pink to brownish skin and body fluids colour change but clears after 6-12 months after stoppage, depression, increased blood sugar, git lining swelling🡪 paralytic ileus, git bleeding, bowel obstruction, splenic infarction

**DOSE;** Adult: 300 mg once a month, to be administered under supervision and 50 mg daily, to be self-administered, alternatively 300 mg once a month, to be administered under supervision and 100 mg once daily on alternate days, to be self-administered

**Uses**

* Treats sulfone-resistant leprosy or to patients who are intolerant to sulfones.
* It also exerts an anti-inflammatory effect and prevents erythema nodosum leprosum, which can interrupt treatment with dapsone.This is a major advantage over other antileprosy drugs. Ulcerative lesions caused by Mycobacterium ulcerans respond well to clofazimine.
* It also has some activity against M. tuberculosis and can be used as last resort therapy for the treatment of MDR tuberculosis.

**Ethionamide and Prothionamide**

They are weak bacteriocidal against M. leprae and can be used as alternatives to clofazimine in the treatment of MDR leprosy. Both cause GI intolerance and are expensive.

**Bacitracin, Glycopeptide Antibiotics, and the Polymyxins 2hr**

**Examples**

Bacitracin

Colistin sulfate

Polymyxin B

Teicoplanin

Vancomycin

**Glycopeptides: vancomycin , teicoplanin** and **Telavancin ( iv infusion) ,dalbavancin**

**Vancomycin (Vancocin**)

 Its a complex tricyclic glycopeptide antibiotic produced by Streptomyces orientalis, while teicoplanin (Targocid) is derived from (Actinomyces) teichomyceticus.

Teicoplanin has two major components: a phosphoglycolipid (A1) and five chlorine-containing glycopeptides (A2). It is available as an investigational drug.

**MOA**

Are inhibitors of cell wall synthesis.

They bind to the terminal carboxyl group on the Dalanyl- D-alanine terminus of the N-acetylglucosamine- N-acetylmuramic acid peptide and prevent polymerization of the linear peptidoglycan by peptidoglycan synthase enzyme ( alters bacterial cell membrane permeability). They are bactericidal in vitro.

**Antimicrobial Spectrum of gycopeptides**

They are **narrow-spectrum** agents

active against gram-+VE organisms. Like vancomycin, teicoplanin is bacteriostatic against staphylococci, streptococci, and enterococci. Gram-positive rods, such as Bacillus anthracis, Corynebacterium diphtheriae, Clostridium tetani, and Clostridium perfringens.

They are **not** effective against **gram-negative** rods, mycobacteria, or fungi.

**PK.**

Poorly absorbed from the GIT, resulting in high concentrations in the feces. In neutropenic patients and patients with altered G.I mucosa, oral absorption of vancomycin may occur and may 🡺toxicity if rapid infusion or large parenteral doses of the drug are given concomitantly. Administered IV. Peak serum levels are achieved 2 hrs and about 55% is bound to serum protein. Distributes into pleural fluids, pericardium,synavial and bile.

crosses placenta and excreted breast milk

The therapeutic range is a trough concentration between 5 and 15g/mL to avoid side effects.

In normal adults t1/2= 5 -11 hours. With impaired renal function t1/2= 7 -9 days.

The dose must be carefully adjusted to avoid toxicity or ineffective treatment in patients undergoing hemodialysis. excreted unchanged by GFR

**Dose**

I.V infusion for 1hr Vancomycin: Average adult dose is 500-1 g BD, but varies depending on weight, age and renal function.

PO; vancomycin (for treatment of *C. difficile or* enterocolitis) 125 mg qds x 7-10 days.

CHILD > 1 month; 15mg/kg tds. max 2g daily.

After IV administration it diffuses into serous cavities and across inflamed but not normal meninges. It can be used in the treatment of meningitis with susceptible organisms.

It is also given via ventriculoatrial or ventriculoperitoneal shunts when these become infected.

Renal excretion is predominant, with 80 to 90% of an administered dose eliminated in 24 hours.

Only small amounts in the stool and bile after i.v administration.

**Teicoplanin t1/2= 50 hrs**

It is not absorbed from the intestinal tract THUS **not** given po.

Peak plasma levels are achieved about 2 hrs. After i.m administration. The drug distributes widely in tissues; plasma protein binding is about 90%., which is considerably longer than that of vancomycin, and may be useful for outpatient administration. It is excreted by the kidneys.

**DOSE; Teicoplanin i.v/I.M** 6mg-10mg/kg bdx 3days then 6mg/kg o.d. max 800mg/day depending on severity.

 **Clinical Uses**

* Vancomycin and teicoplanin -active against staphylococci and streptococci.
* They are 2ND -line drugs in the treatment of most infections. As antistaphylococcal agents they are less effective than beta-lactam &cephalosporin antibiotics.
* Vancomycin dosage iv /po Adult: 15–20 mg/kg every 8–12 hours or 1 g 12-hrly but varies depending on weight, age and renal function.
* Used to treat methicillin-resistant S. aureus (MRSA) infections, in particular the Staphylococcus epidermidis infections associated with the use of intravascular catheters and in patients with peritonitis who are on continuous ambulatory peritoneal dialysis.
* alternative therapy for the staph. enterocolitis,
* Peritonitis and endocarditis for treatment and prophylaxis active for enteroccoci.
* Peritonitis associated with peritoneal dialysis
* In orthopaedic surgery.
* Complicated skin and soft tissue infections
* Bone infections .Joint infections
* Community-acquired pneumonia, Hospital-acquired pneumonia [including ventilator-associated pneumonia]
* Acute bacterial meningitis

 **Adverse Effects**

The major ADR 🡺ototoxicity leading to tinnitus, high tone hearing loss, and deafness

The IV infusion of vancomycin 🡺chills, fever, and a maculopapular skin rash often involving the head and upper thorax (red man syndrome).

Red man syndrome is associated with increased levels of serum histamine and steven johnsons syndrome

Nephrotoxicity for iv worse if combined with furosemide,aminoglycosides ,amphotericin b

pseudomembranous colitis

Phlebitis

Rapid infusion 🡪 hypotension ,bradycardia ,cardiogenic shock

**Hematological disorders**; thrombocytopenia, leucopenia. Agranulocytosis . dizziness

**Telavancin ( iv infusion)**

a glycopeptide has bactericidal activity against aerobic and anaerobic Gram-positive bacteria including multi-resistant staphylococci. However, there are reports of Staphylococcus aureus with reduced susceptibility to glycopeptides.

**indications**

Hospital-acquired pneumonia, known or suspected to be caused by meticillin-resistant Staphylococcus aureus when other antibacterials cannot be used

**dose;** Adult: 10 mg/kg once daily for 7–21 days.

**SIDE-EFFECTS**

Common ;constipation . diarrhoea . dizziness . headaches . increased risk of

infection . insomnia . nausea . renal impairment . skin reactions . taste altered . urine abnormalities . vomiting

uncommon ;

Altered smell sensation . anaemia . angina pectoris . anxiety . appetite decreased . arrhythmias .

arthralgia . confusion . congestive heart failure . depression, drowsiness . dry mouth . dyspnoea . electrolyte imbalance . eye irritation . flatulence . flushing . gastrointestinal discomfort . haematuria . hearing impairment . hepatitis . hiccups . hyperglycaemia . hyperhidrosis . hypertension . hypoglycaemia . hypotension . laryngeal pain . leucopenia . muscle complaints . nasal congestion . oedema . oral hypoaesthesia . pain . palpitations

**Dalbavancin (iv infusion)**

its a glycopeptide antibacterial ,bactericidal activity against Gram-positive bacteria

including various staphylococci.

**Indications and dose**

Acute bacterial skin and skin structure infection ; Adult: 1500 mg for 1 dose, alternatively 1000 mg, then 500 mg after 1 week

**Side effects**

Common or very common Diarrhoea , headache ,nausea

Uncommon Anaemia . antibiotic associated colitis . appetite decreased , constipation , cough , dizziness . eosinophilia . flushing , gastrointestinal discomfort , increased risk of infection, infusion related reaction .

**BACITRACIN**

* Bacitracin and the polymyxins are polypeptide antibiotics.

They are relatively toxic drugs and have had only limited use in chemotherapy until recently. Bacitracin and the glycopeptides affect cell wall synthesis and treats gram-positive bacteria. The polymyxins affect the cell membrane and treats gram-negative infections and *Pseudomonas aeruginosa*

**Bacitracin/** topical antibiotic

Structure and MOA

Bacitracin is a mixture of polypeptide antibiotics produced by Bacillus subtilis.

It prevents cell wall synthesis by binding to a lipid pyrophosphate carrier that transports cell wall precursors to the growing cell wall.

**Antimicrobial Spectrum of bacitracin**

It inhibits gram-positive cocci, including S.aureus, streptococci, a few gram-negative organisms, and one anaerobe, Clostridium difficile.

**PK**-Bacitracin is a topical antibiotic. The bacitracins are not absorbed from the gastrointestinal tract following oral administration.

**Clinical Uses of bacitrcin**

Highly active against staphylococci, Streptococcus pyogenes, and C. difficile.

It’s active against the group A streptococci is used in the laboratory as a means of differentiating between the Lancefield group A streptococci and other streptococci. Well tolerated topically and orally and is frequently used in combination with other agents like neomycin creams.

Effective in the treatment of impetigo and other superficial skin infections.

**THE POLYMYXINS**

The polymyxins are a group of antibiotics produced by *Bacillus polymyxa.*

*examples* Polymyxin B (*Aerosporin*) and colistin (polymyxin E, *Coly-Mycin*) are used in the treatment of bacterial diseases.

***Structure and Mechanism of Action***

They are polypeptide antibiotics that contain both hydrophilic and lipophilic regions.

These antibiotics accumulate in the cell membrane and interact with membrane phospholipids, the fatty acid portion of the antibiotic penetrates the hydrophobic portion of the membrane phospholipid and the polypeptide ring binds to the exposed phosphate groups of the membrane. 🡪 distortion of the membrane, impair its selective permeability, produce leakage of metabolites, and inhibit cellular processes. These antibiotics also are toxic to mammalian cells.

**Antimicrobial Spectrum**

They are against facultative gram-negative bacteria, *P. aeruginosa* in particular.

**pk;**

Polymyxin B and colistin are **not** well absorbed from the gut. An i.m injection of the polymyxins results in high drug concentrations in the liver and kidneys, but the antibiotic does not enter the cerebrospinal fluid (CSF), even in the presence of inflammation.

They are slowly excreted by glomerular filtration; the slow elimination rate is due to binding in tissues. Elimination is decreased in patients with renal disease, and drug accumulation can lead to toxicity.

Sodium colistimethate, the parenteral preparation, binds less to tissue and is excreted faster than the free base.

***Clinical Uses***

Broad-spectrum antibiotics,

Their only justifiable use may be as topical agents.

In combination with neomycin, polymyxin B can be used as a bladder irrigant to reduce the risk of catheter associated infections, although this use remains controversial.

Topical therapy in external otitis caused by *P. aeruginosa.*

**Adverse Effects**

Nephrotoxicity when used parenterally, and any preexisting renal insufficiency will potentiate the nephrotoxicity

Neurotoxicity is a rare adverse reaction that can be recognized by perioral paresthesia, numbness, weakness, ataxia, and blurred vision.

They precipitate respiratory arrest both in patients given muscle relaxants during anesthesia and in persons with myasthenia gravis.

|  |  |  |  |
| --- | --- | --- | --- |
| **Week 9:** |  |  | **CATs** |
| **Week 10:** |  |  | **Antifungal Agents;**classification and mechanisms of action,polyenes – amphotericin B, nystatin; heterocyclic benzfuran (griseofulvin). |
| **Week 11** |  |  | **Antifungal Agents;**antimetabolites (flucytosine),imidazoles (ketoconazole, clotrimazole), triazoles (fluconazole, itraconazole). |
| **Week 12:** |  |  | **Antifungal Agents;**echinocandins (caspofungin, anidulafungin, micafungin),allylamines (terbinafine), other topical antifungals. |

**Antifungal Drugs**

**Examples of antifungals**

Amphotericin B

Butoconazole

Capsofungin

Ciclopirox

Clotrimazole

Econazole

Fluconazole

Flucytosine

Griseofulvin

Itraconazole

Ketoconazole

Miconazole

Nystatin

Oxiconazole nitrate

Sulconazole nitrate

Terbinifine hydrochloride

Naftifine

Terconazole

Tioconazole

Tolnaftate

Undecylenic acid

Voriconazole

**Introduction**

Fungal infections are usually more difficult to treat than bacterial infections, because fungal organisms grow slowly and fungal infections often occur in tissues that are poorly penetrated by antimicrobial agents. Therapy of fungal infections usually requires prolonged treatment.

**Making a choice of antifungal drugs (2hrs)**

* Spectrum
* Likely pathogens
* Documented pathogens
* Site of infection
* Concomitant diseases
* Hepatic/renal function
* Toxicities
* Drug Interactions
* IV/PO
* Cost

**Classification**

1. **according to antifungal antibiotics**
* polyenes macrolide e.g amphotericin B and nyst**atin**
* benzofuran e.g griseofulvin
1. **according to synthetic**
2. azoles;
* triazoles. e.g fluconazole, itraconazole, voriconazole
* imidazoles. e.g ketoconazoles, miconazoles,clotrimazole.
1. anti metabolites / fluorinated pyrimidine e.g flucytosine
2. expoxides inhibitors or allylamines e.g terbinafine, naftifine
3. echinocandins e.g caspofungin, micafungin
4. **according to the route of administration**
5. systemic antifungals
* Membrane disrupting agents e.g Amphotericin B
* Ergosterol synthesis inhibitors e.g Azoles ( Fluconazole, ketoconazole)
* Nucleic acid inhibitor e,g Flucytosine
* Glucan synthesis inhibitors e.g Echinocandins ( caspofungin)
* expoxides inhibitors or allylamines e.g terbinafine
* benzofurans; griseofulvin,
1. Topical in candidiasis e.g imidazoles like ketoconazole and miconazole. Triazoles like terconazole. polyenes like nystatin and amphotericin B, GV

Topical dermatiphytes e.g expoxides inhibitors like terbinafine and neftifine. Whitefield ointment that has 12% benzoic acid and 6% salicylic acid

1. **according to antifungal antibiotics (2hrs)**
2. **polyenes macrolide**
3. **Amphotericin b** (Fungizone)

**Chemical structure;** a polyene antifungal drug produced by the actinomycete Streptomyces nodosus, consists of a large ring structure with both hydrophilic and lipophilic regions.

 **MOA**

it binds to the fungal cell membrane component ergosterol🡪 increased fungal cell membrane permeability and the loss of intracellular constituents🡪cell death. also binds to cholesterol🡪side effects.

**Antifungal Spectrum**

Treats systemic disseminated fungal infections caused by Candida spp., Cryptococcus neoformans, and the invasive dimorphic fungi (Aspergillus spp., Histoplasma capsulatum, Coccidioides immitis, Blastomyces dermatitidis, and Sporothrix schenckii).

IV amphotericin B remains the treatment of choice for serious invasive fungal infections unresponsive to other agents.

**Mechanism of resistance**

* reduced ergosteral content ( erg 2or erg 3 )genes
* alteration in steral content or the affinity
* reorientation or masking of ergosteral
* stationary growth of organism
* previous exposure to azoles

**PK;**

* It is an IV drug or intrathecal, intraarticular, topical eye drops.
* After infusion the drug is rapidly taken up by the liver and other organs and is then slowly released back into the circulation.
* 90% of the drug is bound to protein, with apparently poor penetration to tissues and body fluids
* Its initial half-life is about 24 hrs; the second elimination phase has a half-life of 15 days.
* The initial phase comprises elimination from both a central intravascular and a rapidly equilibrating extravascular compartment.
* The 2nd longer phase represents elimination from storage sites in a slowly equilibrating extravascular compartment.
* Drug concentrations in pleural fluid, peritoneal fluid, synovial fluid, aqueous humor, and vitreous humor approach two-thirds of the serum concentration when local inflammation is present.
* The major route of elimination of amphotericin B is by metabolism, with little intact drug detected in urine or bile.

**Clinical Uses**

1. Used to treat serious disseminated yeast and dimorphic fungal infections in immune compromised hospitalized patients.
2. For the unstable neutropenic patient with Candida albicans fungemia
3. For the AIDS patient with moderate to severe cryptococcal meningitis.
4. For the AIDS patient with disseminated histoplasmosis
5. Its preferred for initiation treatment, but once infection is controlled, daily oral itraconazole is preferred
6. Most forms of blastomycosis and sporotrichosis in normal hosts no longer require amphotericin B treatment.

**Dose**

A dose of 1.0–1.5 mg/kg daily depending on disease severity and appearance of nephrotoxicity, infused over 2–4 hours. Hydrocortisone or chlorpheniramine can reduce febrile reactions and

chlorpromazine can reduce nausea.

Loading the patient with normal saline before giving the drug may reduce nephrotoxicity.

Liposomal amphotericin requires higher doses of 3–6 mg/kg.

**Drug interaction**

Avoid the concomitant giving of other nephrotoxic agents, such as aminoglycosides and diuretics.

hypokalemia with digoxin therapy

**ADR**

* Nausea, vomiting, and anorexia .
* Fever, chills, and tachypnea occur shortly after the initial IV doses of
* Continued administration of amphotericin B thus needs premedication with acetaminophen, aspirin, and/or diphenhydramine or addition of hydrocortisone to the infusion bag.
* Nephrotoxicity is the most common
* Hypokalemia and hypomagnesemia due to Wasting of potassium and magnesium in the urine secondary to renal tubular acidosis and necessitates oral replacement of these minerals and hydrating patients with saline infusions prior to its dosing have been advocated.
* Hematologic; Normochromic normocytic anemia, thrombocytopenia and leukopenia.
* Infusion of the drug into a peripheral vein usually causes phlebitis or thrombophlebitis.
1. **Nystatin (*****Mycostatin*)**

It is a polyene antifungal drug with a ring structure similar to that of amphotericin B and a mechanism of action identical to that of amphotericin B.

Too toxic for systemic use.

Limited to the topical treatment of superficial infections caused by *C. albicans.* Infections commonly treated are oral candidiasis (thrush), mild esophageal candidiasis, and vaginitis.

**antifungal antibiotic**

**benzofuran; griseofulvin (Gris-PEG, Grifulvin, Grisactin, Fulvicin)**

Produced by the mold Penicillium griseofulvin

Oral fungistatic agent used in the long-term therapy of dermatophyte infections by *Epidermophyton,* *Microsporum,* and *Trichophyton* spp.

**MOA;**

its fungistatic thus given for weeks or months.

Inhibits fungal growth by binding to the microtubules responsible formitotic spindle formation, leading to defective cell walldevelopment. only active against dermatophytes.

**PK;**

* Ineffective topically, administered orally but has poor gastrointestinal absorption.
* Absorption can be improved by taking the drug with fatty meals.
* Peak serum levels occur 4 hrs after dosing.
* Metabolized in the liver and has a half-life of 24 - 36 hrs.
* It binds to keratin precursor cells and newly synthesized keratin in the stratum corneum of the skin, hair, and nails, stopping the progression of dermatophyte infection.
* Duration of therapy is 4 to 6 weeks of therapy for skin and beard ringworms.

 **ADR**

* Griseofulvin is usually well tolerated. Headache is common with initiation of therapy.
* Hepatotoxicity (especially in patients with acute intermittent porphyria), dermatitis, and gastrointestinal distress also occur.

**drug Interactions**

* It diminishes the anticoagulant effect by enzyme induction increasing warfarin metabolism.
* Barbiturates like phenobarbital lead to griseofulvin treatment failure by enzyme induction🡪 its increased metabolism.
* Griseofulvin can precipitate porphyria.

 **b) According to synthetic antiofungals**

**i) THE AZOLES (2hrs)**

Azole antifungal drugs are synthetic compounds with broad-spectrum fungistatic activity. They are antibacterial, antiprotozoal, anti -helminthic and antifungals

Two groups

* Older imidazole agents, in which the five-member azole nucleus contains 2 nitrogens
* Triazole compounds, fluconazole and itraconazole, in which the azole nucleus contains 3 nitrogens.

**MOA**

Binding to cytochrome P450 enzymes responsible for the demethylation of lanosterol to ergosterol. Reduced fungal membrane ergosterol concentrations result in damaged, leaky cell membranes. The toxicity of these drugs depends on their relative affinities for mammalian and fungal cytochrome P450 enzymes. The triazoles have fewer side effects, better absorption, better drug distribution in body tissues, and fewer drug interactions.

**Resistance to azoles**

* single point mutation of erg 11 gene
* production of low affinity sterals.
* increased production of lanosteral demethylase enzyme.
* changes in steral or phospholipid composition of the cell membrane🡪 decreased permiability

**side effects**

headache, visual disturbance, hepatotoxicity, resistant hypertension.

1. **Triazoles**

**Fluconazole (Diflucan) po, iv**

**pk**;

* it does not require an acidic environment, as does ketoconazole, for gastrointestinal absorption.
* About 80 to 90% of an orally administered dose is absorbed, yielding high serum drug levels. The half-life is 27 - 37 hrs, permitting once daily dosing in patients with normal renal function.
* Only 11% of circulating drug is bound to plasma proteins.
* The drug penetrates widely into most body tissues, including normal and inflamed meninges. CSF levels are 60 - 80% of serum levels, permitting effective treatment for fungal meningitis.
* About 80% of the drug is excreted unchanged in the urine, and 10% is excreted unchanged in the feces.
* Dosage reductions are required in the presence of renal insufficiency.

**Clinical Uses**

* Fluconazole is very effective in the treatment of infections with most Candida spp.
* AIDS patients with esophageal candidiasis.
* A single 150-mg dose has been shown to be effective treatment for vaginal candidiasis.
* A 3-day course is effective treatment for Candida urinary tract infection.
* For bladder irrigation.
* Preliminary findings suggest that Candida endophthalmitis
* Stable non-neutropenic patients with candidemia
* initial treatment of mild cryptococcal meningitis
* prevention of relapsing meningitis

 **ADR**

* Nausea, vomiting, abdominal pain, diarrhea, and skin rash in <3% of patients.
* Asymptomatic liver enzyme elevation and drug associated hepatic necrosis.
* Alopecia has been reported in patients receiving prolonged high-dose therapy.
* teratogenic

**drug interraction**

* Co-administration of fluconazole with phenytoin results in increased serum phenytoin levels.

**Itraconazole (Sporanox) (po or iv)**

**pk**; is lipophilic and water insoluble and requires a low gastric pH for absorption.

Distribites to bones and adipose tissues. Oral bioavailability is variable, only 50 to 60% when taken with food and 20% or less when the drug is taken on an empty stomach. Highly protein bound (99%), metabolized in the liver and excreted into the bile. inhibits cpy-p-450 reversibly.

 With initial dosing, the plasma T1/2= 15 to 20 hrs; steady-state serum concentrations are reached only after 2 weeks of therapy, when the half-life is extended to 30 to 35 hours. In lipophilic tissues, drug concentration is 2 to 20 times that found in serum. Drug does not appear in significant quantities in the urine and. **cannot** cross BBB

**Clinical Uses/ indications and dose**

* Vulvovaginal candidiasis po: 200 mg twice daily for 1 day
* all forms of sporotrichosis except meningitis
* Vulvovaginal candidiasis (recurrent) po: 50–100 mg daily for 6 months
* Oral or oesophageal candidiasis that has not responded to fluconazole po: 100–200 mg twice daily for 2 weeks (continue for another 2 weeks if no response; the higher dose should not be used for longer than 2 weeks if no signs of improvement)
* Oral or oesophageal candidiasis in HIV-positive or other immunocompromised patients
* Systemic candidiasis where other antifungal drugs inappropriate or ineffective po: 100–200 mg once daily ,iv : 200 mg every 12 hours for 2 days, then 200 mg od for max. 12 days
* Systemic candidiasis (invasive or disseminated) where other antifungal drugs inappropriate or ineffective po: 200 mg twice daily
* Pityriasis versicolor; po: 200 mg once daily for 7 days
* dermatophyte infections
* Tinea pedis | Tinea
* long-term suppressive treatment of disseminated histoplasmosis in AIDS
* cryptococcal and coccidioidal meningitis
* Tinea corporis | Tinea cruris po: 100 mg od for 15 days, alternatively 200 mg od for 7 days
* Onychomycosis po: 200 mg once daily for 3 months, alternatively 200 mg twice daily for 7 days, subsequent courses repeated after 21-day intervals; fingernails 2 courses, toenails 3 courses
* Aspergillosis
* blastomycosis
* Systemic aspergillosis where other antifungal drugsinappropriate or ineffective dose as below
* Prophylaxis of deep fungal infections (when standard therapy inappropriate) in patients with haematological malignancy or undergoing bone-marrow transplantation who are expected to become neutropenic po: 5 mg/kg daily in 2 divided doses, to be started before transplantation
* Histoplasmosis po Adult: 200 mg 3 times a day for 3 days, then 200 mg 1–2 times a day iv Adult: 200 mg bd for 2 days, then 200 mg once daily for max. 12 days
* Systemic cryptococcosis including cryptococcal meningitis where other antifungal drugs inappropriate or ineffective po or iv : 200 mg once daily, dose increased in invasive or disseminated disease and in cryptococcal meningitis, increased to 200 mg twice daily for 12 days
* Maintenance in HIV-infected patients to prevent relapse of underlying fungal infection and prophylaxis in neutropenia when standard therapy inappropriate

**ADR**

* Nausea and epigastric distress.
* Dizziness and headache also have been reported.
* High doses may cause, hypertension, and edema.
* Hepatotoxicity occurs in fewer than 5% of cases and is usually manifested by reversible liver enzyme elevations.
* With iv use ; Chest pain . confusion . cough .
* electrolyte imbalance ( hypokalemia) . fatigue .
* granulocytopenia . hyperglycaemia . hyperhidrosis . hypersensitivity . hypertension . myalgia . pain . renal impairment . tachycardia . tremor . urinary incontinence
* ▶ Uncommon; With iv use Dysphonia . hearing loss . numbness . thrombocytopenia With oral use Flatulence . menstrual disorder
* ▶ Rare or very rare; With oral use Erectile dysfunction . hearing impairment . leucopenia . sensation abnormal . serum sickness . urinary frequency increased

**Drug Interactions**

Interacts with drugs that are metabolized by cpy p-450, e.g. rifampin, phenytoin, and carbamazepine.

May affect the metabolism of oral hypoglycemic agents and coumadin.

It raises serum digoxin and cyclosporine levels

Absorption is impaired by antacids, H2 blockers, proton pump inhibitors, and drugs that contain buffers, such as the antiretroviral agent didanosine. itraconazole, ketoconazole require acidic ph for absoption

**Doses;**

* Itraconazole: 100–200 mg orally, daily single dose. severe infection 200 mg IV 12h x 4 doses, then 200 mg IV 24h. followed by 200 mg PO 12h oral solution
* Fluconazole: 100–400 mg orally or by i.v. infusion, daily single dose (max1600mg).

6 mg/kg/d for susceptible strains (400 mg/d) or 12 mg/kg/d (800mg)

* Voriconazole: 100mg-200 mg orally b.d. An i.v. 6 mg/kg IV 12h x 2 doses, then 4 mg/kg IV 12h

Oral (>95% bioavailability on empty stomach)

<40 kg – 100 mg PO q12h

>40 kg – 200 mg PO q12h

**Voriconazole (Vfend), ( iv or po)**

 A synthetic derivative of fluconazole, is a 2nd -generation triazole with improved antifungal activity against Aspergillus and Fusarium spp., P. boydii, Penicillium marneffei, and fluconazole-resistant Candida spp.

**pk;** Ha**s** high oral bioavailability and good CSF penetration.

Undergoes extensive hepatic metabolism and highly protein bound

Dosage reduction is necessary with severe hepatic insufficiency but not with renal insufficiency.

**Drug interactions**

cyclosporins (increased cyclosporine levels).

phenytoin, rifampin, and rifabutin (decreased voriconazole levels). Because of its low toxicity profile, this drug may gain importance in the chronic treatment of infections with invasive dimorphic fungi and resistant Candida spp.

**Indications**

* Invasive aspergillosis
* Esophageal candidiasis
* Fungal infections caused by Scedosporium apiospermum and Fusarium spp.

**dose po/ iv** 4mg/kg bd daily or 200mg-400mg bd

**adverse reactions ;**

Common or very common

visual disturbance eye disorders . eye inflammation , rashes,

increased liver enzymes hepatic disorders

Acute kidney injury .

hematological🡪agranulocytosis . haemorrhage, leucopenia, thrombocytopenia alopecia . anaemia . .

.bone marrow disorders . chills . skin reactions . fever .

git discomfort; vomiting . constipation . diarrhoea .

respiratory; dyspnoea 🡪pulmonary oedema . chest pain.

hypoglycaemia . electrolyte imbalance .

increased risk of infection .muscle tone increased .

cns;🡪seizure . sensation abnormal confusion . tetany . tremor . insomnia. asthenia, anxiety drowsiness depression .hallucination headache . syncope

cvs;🡪arrhythmias, hypotension oedema disorders

▶ Uncommon Adrenal insufficiency . arthritis . brain oedema

duodenitis . encephalopathy . eosinophilia . gallbladder

disorders . hearing impairment . hypothyroidism .

influenza like illness . lymphadenopathy . lymphangitis .

movement disorders . nephritis . nerve disorders .

pancreatitis . parkinsonism . phototoxicity . proteinuria .

pseudomembranous enterocolitis .QT interval

prolongation . renal tubular necrosis

1. **imidazoles**

**Ketoconazole** tabs 200–400 mg orally, daily single dose.

**pk**;

Unlike other imidazoles, ketoconazole (Nizoral) can be absorbed orally, but it requires an acidic gastric environment; patients concurrently treated with H2 blockers or who have achlorhydria have minimal drug absorption. Serum protein binding exceeds 90%.

Metabolized in the liver and excreted in the bile.

The initial half-life is 2 hours; 8 - 12 hrs after ingestion, the half-life increases to 9 hours.

Penetration into CSF is negligible, so that the drug is ineffective in the treatment of fungal meningitis.

Note; Small amounts of active drug appear in the urine thus not effective in the treatment of Candida cystitis.

**Clinical Uses**

* treatment of cutaneous and mucous membrane dermatophyte and yeast
* Effective in the treatment of thrush
* Treatment of vulvovaginal candidiasis with topical imidazoles is less expensive.

**Adverse Effects**

* Nausea, vomiting, and anorexia
* Epigastric distress can be reduced by taking ketoconazole with food.
* Pruritis and/or allergic dermatitis occur in 10% of patients.
* Liver enzyme elevations though hepatitis is rare.
* Reduction in testosterone synthesis and blocks the adrenal response to corticotropin leading to Gynecomastia, impotence, reduced sperm counts, and diminished libido can occur in men, and irregular menses in women. These hormonal effects have led to the use of ketoconazole as a potential adjunctive treatment for prostatic carcinoma.

**Drug Interactions**

* Both rifampin and isoniazid lower plasma ketoconazole levels, and concomitant administration should be avoided.
* Phenytoin serum levels should be monitored closely when ketoconazole is prescribed.
* It increases in serum concentrations of warfarin, cyclosporine, and sulfonylureas.
* Because of its ability to increase serum cyclosporine levels, ketoconazole has been given to cyclosporine- dependent cardiac transplant recipients to reduce the dose of cyclosporine needed and as a cost-saving measure. H2 blockers and antacids decrease its absorption

**miconazole**

Miconazole (Monistat) is a broad-spectrum imidazole antifungal agent used in the topical treatment of cutaneous dermatophyte infections and mucous membrane Candida infections, such as vaginitis. Minimal absorption occurs from skin or mucous membrane surfaces.

Local irritation to skin and mucous membranes can occur with topical use; headaches, urticaria, and abdominal cramping have been reported with treatment for vaginitis.

**clotrimazole**

Clotrimazole (Lotrimin, Gyne-Lotrimin, Mycelex) is a broad-spectrum fungistatic imidazole drug used in the topical treatment of oral, skin, and vaginal infections with C. albicans. It is also employed in the treatment of infections with cutaneous dermatophytes.

Topical use results in therapeutic drug concentrations in the epidermis and mucous membranes; less than 10% of the drug is systemically absorbed. Although clotrimazole is generally well tolerated, local abdominal cramping, increased urination, and transient liver enzyme elevations have been reported.

**OTHER IMIDAZOLES**

These are topical imidazoles available for the treatment of cutaneous and mucous membrane candidiasis, ringworm, and tinea versicolor.

**Butoconazole (*Femstat*)**; effective topical agent for vaginal candidiasis;

**terconazole (*Terazol*)** ; effective in the treatment of vaginal candidiasis;

**econazole (*Spectazole*)**; treatment of superficial fungal infections of the skin, achieving high tissue levels in the stratum corneum.

**Oxiconazole nitrate (*Oxistat*) and sulconazole nitrate (*Exelderm***); treatment of dermatophyte infections and pityriasis (tinea versicolor).

**Tioconazole (*Vagistat*)**; the treatment of dermatophyte infections and candidiasis.

All of these agents have minimal systemic absorption when applied topically, but occasionally use of these drugs can result in systemic toxicity.

ii) **Antimetabolite**

**Flucytosine** (**5-fluorocytosine (5-FC)**

It is a synthetic pyrimidine antimetabolite cytotoxic drug used in combination with amphotericin B and itraconazole

**MOA**

* It is systemic fungistatic.
* interferes with fungal DNA synthesis and protein synthesis
* It is a fluorinated pyrimidine analogue of cytosine that was originally synthesized for use as an antineoplastic agent. 5-FC is converted to 5-fluorouracil inside the cell by the fungal enzyme cytosine deaminase. 5-FC metabolites interfere with fungal DNA synthesis by inhibiting thymidylate synthetase enzyme. Incorporation of these metabolites into fungal RNA 🡪inhibition of protein synthesis.

**Pk;**

Absorbed orally, with greater than 90% bioavailability. The serum half-life is 3 - 5 hrs, with serum levels peaking 4 to 6 hours after a single dose.

The drug is widely distributed in body fluids, with CSF fluid levels 60 to 80% of serum levels.

It penetrates well into urine, aqueous humor, and bronchial secretions.

Minimal serum protein binding allows more than 90% of each dose to be excreted in the urine;

Dosage reductions are required in the presence of renal impairment. 5-FC can be removed by both hemodialysis and peritoneal dialysis. 5-FC conversion to toxic metabolites may occur in mammalian cells to a limited extent, which accounts for 5-FC toxicity.

**Clinical Uses**

* Active against C. albicans,
* Combination therapy for systemic candidiasis and cryptococcal meningitis and as an alternative drug for chromomycosis.
* When it is used as monotherapy, resistance and clinical failure are common.
* Combination therapy with amphotericin B and flucytosine for therapy of cryptococcal meningitis and deep-seated Candida infections, such as septic arthritis and meningitis

**dosage;**

as an adjunct in systemic yeast infection to amphotericin in severe systemic candidiasis and in other severe or long-standing infections Iv infusion: Usual dose 200 mg/kg daily in 4 divided doses usually for not more than 7 days or

100–150 mg/kg daily in 4 divided doses, lower dose may be sufficient for extremely sensitive organisms

Cryptococcal meningitis (adjunct to amphotericin) iv infussionn: 100 mg/kg daily in 4 divided doses for 2 weeks

**Adverse Effects**

* Skin rash, epigastric distress, diarrhea,
* Liver enzyme elevations
* alopecia
* Concurrent amphotericin B therapy rises blood levels of 5-FC leading to bone marrow toxicity and leukopenia and thrombocytopenia results. serum levels should be closely monitored in patients with renal insufficiency.
* Leukopenia; thus not tolerated by end-stage HIV infected patients with disseminated fungal infection.
* Teratogenic

**Echinocandins** example; **capsofungin ( iv infusion)**

Capsofungin (*Cancidas*) is a semisynthetic lipo peptide known as an echinocandin.

**MOA**

Inhibits the synthesis of cell membrane.

It acts as a non-competitive inhibitor of the synthesis of 1,3-ß-glucan, a polysaccharide in the cell wall of

many fungi🡪cell death. N/B; Glucans are essential in maintaining osmotic integrity of fungal cell wall.

**spectrum of activity** Capsofungin has in vitro activity fungistatic against *Aspergillus* *fumigatus, Aspergillus flavus,* and *Aspergillus terreus;* cidal on *candida spp, pneumocystic carinii.* ***NO*** *activity on cryptococcus*

**Uses**

Treatment of invasive aspergillosis in patients not responding to other antifungal agents, e.g amphotericin B, and itraconazole.

**Pk;** not absorbed from the gastrointestinal tract. induces liver enzymes p-450

It is highly protein bound and has a serum half-life of 9 to 11 hours. Metabolized in liver and is not excreted in the urine.

**ADR**

* Mediated through histamine release; these are facial flushing ( erythema), rash, fever, and pruritis.
* Nausea and vomiting have also been reported.
* Dose reductions are required in the presence of moderate hepatic insufficiency.

**Allylamines**

The allylamines (naftifine hydrochloride and terbinafine hydrochloride) are reversible noncompetitive inhibitors of the fungal enzyme squalene monooxygenase (squalene 2,3 epoxidase), which coverts squalene to lanosterol. With a decrease in lanosterol production, ergosterol production is also diminished, affecting fungal cell membrane synthesis and function. These agents generally exhibit **fungicidal** activity against dermatophytes and fungistatic activity against yeasts.

**Naftifine hydrochloride (*Naftin*) cream or gel**; available for topical use only in the treatment of cutaneous dermatophyte and *Candida* infections. used for tinea cruris

**Terbinafine hydrochloride (*Lamisil*)**; for topical and systemic use (oral tablet)

* Treats dermatophyte skin and nail infections for 6- 12weeks
* It exhibits in vitro activity against filamentous and dimorphic fungi
* It is used most commonly in the treatment of onychomycosis.
* It is superior to griseofulvin and at least equivalent to itraconazole.
* Orally is 99% protein bound and accumulates in fat, skin, and nails, persisting for weeks.
* CSF penetration is less than 10%.
* Dosage reductions are required with renal or hepatic insufficiency.
* Has little effect on hepatic cytochrome P450 enzyme systems, it enhances cyclosporine clearance.
* Orally well tolerated but occasionally causes gastric distress and liver enzyme elevation.
* Visual disturbance. Accumulates in breast milk thus not given to lactating mother.

**MISCELLANEOUS TOPICAL ANTIFUNGAL AGENTS**

**Ciclopirox olamine (*Loprox*)** is a pyridone derivative available for the treatment of cutaneous dermatophyte infections, cutaneous *C. albicans* infections, and tinea versicolor caused by *Malassezia furfur.* It interferes with fungal growth by inhibiting macromolecule synthesis.

**Tolnaftate (*Tinactin***) gel ,creams, and powder preps; effective in the topical treatment of dermatophyte infections and tinea.

**undecylenic acid** is fungistatic, requires prolonged administration, and is associated with a high relapse rate.it containing 5% undecylenic acid and 20% zinc undecylenate. Effective in the prevention of recurrent tinea pedis

**Dosages of common po and infusion antifungal drugs**

**Amphotericin B**; iv infusion initial 1mg /30min then 250mcg /kg daily increase in 3-4days then 1mg/kg/day if well tolerated (please *read manufacture instructions before use)*

**Fluconazole; po** or **iv dose;** 3-6mg/kg/day for 2-6 weeks depending on infection invasiveness. 100mg-800mg/day

cryptoccocal infections po/iv infusion day 1= 400mg then 200mg-400mg/day for 8 weeks.max 800mg. child 6-12mg/kg/day max 400mg in neonates give at every 72hrs. prophylaxis 50-200mg/day po/iv

**Flucytosine ;** iv infusion /30min 100-200mg/kg/day in 4 divided doses max duration 7days

**Griseofulvin; po =**500mg/day or in divided doses, child 10-20mg /kg /day or divided doses

**Capsofungin**; iv infusion >18yrs day 1= 70mg then 50mg od/day

**Itraconazole; po/iv**; po 100mg-200mg /day x7 days. onchomycosis 200mg od x 3months.

IV infusion severe infection 200mg every 12hrs for 2 days then 200mg od for 12 days

**Ketoconazole**; po 200mg daily for 3-4weeks . vaginal candidiasis 200mg od x7days

**Nystatin ;po, pessaries;** po 500,000iu qid . child 100,000iu

**Terbinifine hydrochloride; po;** for tineasis >40kg person; 250mg od 2-6 weeks. child half the dose

**Voriconazole po/iv infusion**; >12years po 400mg bd for 2 doses then 200mg bd/day. iv infusion 4-6mg/kg bd for 2 doses then 3mg/kg bd. child 2-12yrs 7mg/kg/day bd