

PHARMACOLOGY

Antimicrobial Agents: Antibacterial Drugs

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(7-8-2007)

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History

Paul Ehrlich (1854 – 1915) coined the word ‘Chemotherapy’ and said that in order to use chemotherapy successfully we must search for a substance which has affinity for the cells of the parasites and a power of killing or suppressing their growth without harming the host.

Alexander Fleming (1928) discovered penicillium fungi which suppressed the bacterial growth in culture.

Gerherd Domagk 1935 linked sulphonamide to prontosil dye.

Antibiotics are substances produced by microorganisms that are antagonistic to the growth or life of other microorganisms. At present many antibiotics in use are either fully synthetic or are produced by chemical modification of natural products and are hence known as **antimicrobial agents (AMA)**.

Antimicrobial agents can be

- a) Antibacterial agents/drugs
- b) Antiviral agents/drugs
- c) Antifungal agents/drugs

Antibacterial Agents

Before discussing the various drugs in this category it is important to list the pathogenic microorganisms.

a) Cocci

i) Gram positive

- Staphylococcus aureus: Abscesses, septicemia, osteomyelitis, endocarditis, bacteremia
- β hemolytic Streptococcus pyogenes: Pharyngitis, otitis media, sinusitis, septicemia, rheumatic fever
- Streptococcus pneumoniae (pneumococcus): Pneumonia, meningitis, sinusitis
- Streptococcus viridans (peptococcus): Bacteremia, endocarditis
- Streptococcus faecalis (enterococcus): Endocarditis, urinary tract infections

ii) Gram negative

Neisseria gonorrhoeae (gonococcus) : Gonorrhea, urethritis, cervicitis

Neisseria meningitidis (meningococcus): Meningitis

b) Bacilli

i) Gram positive

- Clostridium tetani: Tetanus
- Clostridium perfringens: Gas gangrene
- Clostridium difficile: Pseudomembranous colitis
- Corynebacterium diphtheriae: Diphtheria
- Listeria monocytogenes: Bacteremia, meningitis
- Bacillus anthracis: Pneumonia

ii) Gram Negative (Enterobacteriaceae)

- Escherichia coli: Urinary tract infections,
- Salmonella typhi: Food poisoning, typhoid fever, paratyphoid fever
- Shigella: Gastroenteritis, bacillary dysentery
- Klebsiella: Pneumonia, Urinary Tract Infections
- Proteus vulgaris, Proteus mirabilis: Urinary tract infections
- Enterobacter: Urinary tract infections
- Helicobacter pylori: Peptic ulcers

c) Miscellaneous

- Acinetobacter: Nosocomial opportunistic infections
- Bordetella pertussis: Whooping cough
- Bacteroids fragilis: Abscess in the lungs, brain, infections in the mouth
- Brucella abortus: Brucellosis
- Campylobacter: Gastroenteritis
- Francisella tularensis: Tularemia
- Fusobacterium: Gingivitis, lung and alveolar abscess
- Haemophilus influenza: Sinusitis, bronchitis, meningitis pneumonia
- Haemophilus ducreyi: Ulcers on the genitals and sexually transmitted disease
- Legionella pneumophila: Legionnaire's disease
- Pseudomonas aeruginosa: Pneumonia, urinary tract infection hospital acquired infection in burns patients
- Serratia: Nosocomial opportunistic infections
- Yersinia pestis: Plague

Mechanism of Action

Antibacterial agents have selective toxicity against the infecting organisms and may act by

- a) Destroying the microorganism i.e.; they are **bactericidal drugs**
- b) Inhibiting the growth of the organism i.e.; they are **bacteristatic drugs**

These agents primarily act by

- 1) Inhibiting cell wall synthesis e.g; Penicillins, Cycloserine, Bacitracin
- 2) Damaging/inhibiting the cell membrane function e.g.; Polymixins, collistins, Polyene antibiotics and detergents
- 3) Inhibition of Protein synthesis and impairment of ribosomal functions.
These can act on the 30S subunit e.g.; Streptomycin, Tetracycline or on the 50S subunit like Chloramphenicol, Macrolides, Clindamycin. Lincomycin..
- 4) Inhibition of
 - a) nucleotide synthesis there by interfering with the transcription and translation of genetic information e.g.; Quinolones, Metronidazole, Rifampicin, Ethambutol.
 - b) folic acid synthesis e.g.; Sulphonamides, Trimethoprim

Limitations of antimicrobial use in the clinical practice

1) Development of bacterial resistance to antimicrobial agents.

- a) This is very important factor which may limit the use of antimicrobial agents. Bacterial resistance may be natural or acquired genetically, through the transfer of genetic material by the extra chromosomal plasmids, or through the process of conjugation, or transduction by means of a virus infecting the bacteria or by transformation or incorporation from the environment of free DNA into the bacterial genome making the microorganism resistant to antimicrobial agents
- b) Microorganisms may synthesize enzymes to inactivate the antibiotics e.g.; phosphorylation or acetylation of aminoglycosides; β lactam ring of penicillin being hydrolyzed by β lactamases produced by the resistant microorganisms; Chloramphenicol being inactivated by chloramphenicol acetyl transferases
- c) Decreased drug accumulation in the bacterial cell by decreasing the passage of the drug into the bacterial cell or by increasing the efflux of the drug from the microorganism e.g.; *Pseudomonas aeruginosa*, aminoglycosides, chloramphenicol, Polymyxins
- d) Modification of the target site on the bacteria such that the antimicrobial agent is rendered ineffective e.g.; methicillin resistant *Staphylococcus aureus* (MRSA), Penicillins, aminoglycosides, erythromycin, Rifampicin.
- e) The microorganisms developing alternative metabolic pathway circumventing the use of the antimicrobial agent e.g.; *Staphylococcus* resistant to Sulphonamides, trimethoprim

2) Development of cross resistance: microorganisms developing resistance to certain antimicrobial agents also develop resistance to other chemically related agents e.g.; sulphonamides, Tetracyclines, aminoglycosides, β lactam antimicrobial agents.

3) Super- infections Treatment with antimicrobial agents may lead to suppression of normal bacterial flora or commensal in the Genitourinary tract, Gastro-intestinal tract and respiratory tract leading to overgrowth of pathogenic microorganisms like proteus, staphylococcus, *Pseudomonas*, *Clostridium difficile*, *Candida* as these organisms are free from any competition in the local area. This could lead to serious consequences e.g.; antibiotic associated pseudomembranous colitis due to *Clostridium difficile* super infection. Antimicrobial agents known to cause super- infections include lincomycin, amoxicillin, ampicillin, clindamycin and cephalosporins

In addition opportunistic infections may be seen when the patients immune system is compromised by drugs e.g.; corticosteroids, cancer chemotherapy, or in patients with leukemia and AIDS. Organisms seen in such cases are those that are seldom pathogenic to humans e.g.; *Pneumocystis carinii*, *staphylococcus sp*

Steps taken to prevent of bacteria from developing resistance: Steps may be taken to prevent or limit the development of resistance by rational use of antimicrobial agents. These measures include:

- a) Judicious use of antimicrobial agents. Ensuring that the choice of the antimicrobial agent is appropriate, and is for the right indication and given in the right dose for the appropriate duration of time.

- b) Use of AMA in combination for appropriate conditions e.g., TB, Leprosy, AIDS
- c) Constant monitoring of drug resistant pattern in both hospital and community acquired infections
- d) Avoiding or limiting the use of AMA esp. the newer antimicrobial agents

Use of antimicrobial agents in combination: In most cases of infection treatment with a single AMA is sufficient. However, there are specific indications for the use of AMA in combinations. There indications are:

- a) To prevent development or emergence of resistant strains of microorganisms esp. in chronic infection e.g. TB, Leprosy, AIDS
- b) To widen or enhance the antibacterial spectrum of activity in cases of mixed infection as in peritonitis or septicemia, brain abscess, bronchiectasis
- 3) To increase the antibiotic activity in order to potentiate the effect e.g. Sulphonamide and trimethoprim; Penicillin and Gentamicin in enterococcus endocarditis; amoxicillin and clavulanic acid; Gentamicin and Carbenicillin in Pseudomonas infections.
- 4) Mixed bacterial infections e.g; intra-abdominal infections, genitourinary tract infections.

Ensure that the combination always contains bacteriostatic agents or bactericidal agents. Using a bacteriostatic drug along with a bactericidal agent may lead to antagonism of the antimicrobial activity.

Chemoprophylaxis: May be used

- i) in healthy person to prevent infection to one specific organism
 - ii) to suppress existing infection
- a) Tuberculosis, malaria- chemoprophylaxis is used to suppress any existing infection from becoming overt.
 - b) To prevent spread of infection amongst contacts e.g; school children during a break of meningococcal meningitis
 - c) Chemoprophylaxis during Surgery especially involving the gastrointestinal tract, Gynecological surgeries, amputations, insertions of prosthetic joints, etc. High doses of AMA is administered IV or IM just before (12-24 hrs) or at the time of induction of anesthesia.

Choice of Antimicrobial Agent: The right choice of antimicrobial agent depends on the nature of infection and the sensitivity pattern in the local regional hospital. The duration of treatment also depends on whether the infection is acute, sub acute or chronic or if the AMA is being used for prophylactic or for prevention of infections.

Misuse of AMA includes over use or under use, or their use when there is no indication for their use e.g;

- a) Infection of viral etiology e.g.; Upper Respiratory tract Infections
- b) Pyrexia of Unknown Origin (PUO) persisting for a prolonged period. It is important to identify the cause rather than treat the condition empirically with an AMA
- c) When the use of the AMA is irrational i.e.; the Dose or duration for which the AMA has been used is inadequate.

- d) In the presence of pus or necrotic tissue AMA should be used only following surgical intervention
- e) AMA should not be prescribed empirically.

Antibacterial Drugs

1. Fluoroquinolones

The first quinolone derivative to be used clinically was a 4 quinolone derivative, nalidixic acid, which was used for the treatment of UTI. In the 1980's the fluorinated derivatives of 4-Quinolones such as ciprofloxacin and its analogues were introduced. These Quinolones had wide antibacterial spectrum of activity and low toxic effects. All these Quinolones are synthetic compounds having bactericidal properties and are effective when administered orally.

Table 1 : List of Fluroquinolones

Norfloxacin, Ciprofloxacin, Ofloxacin, Pefloxacin, Lomefloxacin, Levofloxacin, Fleroxacin, Clinafloxacin, Gatifloxacin, Sparfloxacin, Moxifloxacin, Trovafloxacin, Altrofloxacin, Acroisoxacin, Cinoxacin

Machanism of Action : Fluoroquinolones are rapidly bactericidal. They enter bacterial cells by a process of passive diffusion and inhibit the bacterial DNA replication. They inhibit the bacterial DNA gyrase there by preventing the super coiling of DNA, an important process for compacting the chromosomes into the bacterial cell. In addition in the gram positive bacteria they inhibit the enzyme topoisomerase IV which is responsible for separation of replicated DNA chromosomes.

Spectrum of Activity: *E.Coli, Salmonella Shigella, Neisseria Haemophilus influenzae, Pseudomonas aeruginosa, S. pneumoniae, Mycoplasma legionella, Chlamydia Streptococcus., Staphylococcus. Enterococcus, Mycobacterium tuberculosis, M Avium Complex* in AIDS.

Clinical uses of Fluoroquinolones :

- 1) Urinary Tract Infections due to bacteria, Prostatitis
- 2) Acute diarrheal disease due to *E. Coli, Shigella, Salmonella, Campylobacter*
- 3) Staphylococcal infection of bone and soft tissue. In severe infection addition of Rifampicin is recommended
- 4) Meningoccal infection carrier states and typhoid carriers.

Adverse Effects: Fluoroquinolones are relatively safe and do not need discontinuation of treatment because of the development of adverse effects. Nausea, vomiting diarrhea, occasionally headache dizziness, tremors confusion, insomnia, convulsions, joint pain, skin rash,

alteration in Liver Function Tests, photosensitivity (patient should avoid direct exposure to sunlight) are some of the other adverse effects seen with Fluoroquinolones

Rash, tendonitis, tendon rupture on prolonged use, arthropathy (joint erosion damage to muscle ligament (seen commonly with Ciprofloxacin) Photosensitivity (with Lemofloxacin, Pefloxacin, Gatifloxacin, Moxifloxacin) and ECG alteration (with Levofloxacin, Gatifloxacin, Moxifloxacin) can also manifest with the use of these antimicrobial agents

Therapeutic uses :

- 1) Urinary Tract Infection.(UTI): Norfloxacin, Ciprofloxacin, Ofloxacin, Pefloxacin, Lomefloxacin, Levofloxacin are useful in the treatment of UTI
- 2) Acute bacterial diarrhea: Norfloxacin, Ofloxacin (has activity similar to Cotrimoxazole) and Ciprofloxacin are the Fluoroquinolones of choice
- 3) Staphylococcus infection : Ciprofloxacin, Ofloxacin, Pefloxacin, Norfloxacin are the AMA found useful for this condition
- 4) STD (gonorrhea, Chlamydia, trachomatis, chancroid) : Ciprofloxacin, Ofloxacin, Pefloxacin, Norfloxacin and Lomefloxacin are useful
- 5) Bone and soft tissue infections: Ciprofloxacin, Ofloxacin, Pefloxacin, and Lomefloxacin are useful
- 6) Osteomyelitis : High doses of Ciprofloxacin are used
- 7) Respiratory infections : Ciprofloxacin, Ofloxacin, Pefloxacin, and Lomefloxacin are useful
- 8) Chronic bronchitis, pneumoniae, nosocomial pneumoniae, acute sinusitis, ocular infection: Moxifloxacin, Gatifloxacin, Levofloxacin, Sparfloxacin.
- 9) Meningitis due to Gram negative organism Pefloxacin is indicated
- 10) Chronic bacterial prostatitis : Ciprofloxacin, Ofloxacin, Pefloxacin may be given
- 11) Surgical prophylaxis: Levofloxacin is indicated
- 12) Neutropenic patients: Ciprofloxacin should be considered
- 13) Anthrax infections: Ciprofloxacin,
- 14) Multi drug resistant tuberculosis (MDR TB) : Ciprofloxacin, Ofloxacin, should be considered as treatment alternatives
- 15) Mycobacterium complex infection in AIDS : Sparfloxacin

Following is the dosage schedule and frequency of administration of some of the important quinolones:

	Norfloxacin	Ciprofloxacin	Ofloxacin	Pefloxacin	Lomifloxacin	Sparfloxacin
Dose (mg)	400	500	400	400	400	200
Frequency	BD	BD	BD	BD	OD	OD
t $\frac{1}{2}$ (hrs)	5	4	6	11	8	15-20

Drug Interactions

- Absorption of Fluoroquinolones decreases in the presence of Antacids containing Al^{3+} , Mg^{2+} , Ca^{2+} , Zn^{2+} , Fe^{2+} ions and also in the presence of Sucralfate
- Increase in the blood concentration of theophylline is seen in the presence of some of the quinolones (except Ofloxacin, Levofloxacin, Sparfloxacin and lomefloxacin)
- Increased effect of warfarin is observed with quinolones (except Levofloxacin, Sparfloxacin, where in this interaction is not observed.)
- Quinolones should be used with caution in patient receiving quinolones, amiodarone, Sotalol, Erythromycin, Cisapride, Antidepressants, astemizole as all these drugs show ECG changes when given with quinolones.

Contraindications: Pregnancy, Children, patients with Cardiac Arrhythmias and patient with hypokalemia should not be treated with Fluoroquinolones.

Therapy of Urinary Tract Infections: While treating patients of UTI some of the guiding principles that should be followed are:

- Urine Culture and sensitivity should be done before starting the treatment to ensure rational prescribing.
- Cause of infection needs to be identified and the same should be treated or if possible preventable measures should be taken where ever possible.
- Uncomplicated lower UTI should be treated with short course of low dose AMA therapy.
- Upper UTI should be treated with the appropriate AMA for a longer duration.
- Patients with repeated infections of the urinary tract, resistance to the AMA should be suspected and investigations conducted to identify the appropriate AMA.

Following are some of the AMA's that have been found to be useful in the treatment of UTI: Nalidixic acid, Fluoroquinolone, Ampicillin, Aminoglycosides like Gentamicin, Amikacin, Carboxy penicillin – Carbenicillin, ticarcillin, Cephalexin, Trimethoprim and Cotrimoxazole (which is a combination of Trimethoprim and sulphamethoxazole)

2. Penicillins

Penicillins, cephalosporins and the β lactam AMA like monobactams, carbapenems have a common chemical structure and contains a β lactam ring.

Penicillin was first identified by Alexander Flemming in 1928 while studying variants of staphylococcus organism when he noticed a zone of inhibition in the culture plate. This observation led to the isolation and identification of this AMA

The various AMA in this group are:

Natural Penicillins:

- Acid stable – Pen V Phenoxymethyl penicillin administered orally.
- Acid labile – Penicillin G (Benzyl Penicillins these are administered parentally by intravenous or intramuscular route).
- Procaine penicillin G for I.M. depot injection.

- Benzathine penicillin G administered Intra muscularly (IM) depot preparation.

Semi synthetic Penicillins:

- Penicillinase resistance Penicillins : Methicillin , Oxacillin Cloxacillin dicloxacillin Flucloxacillin (for oral and Intramuscular administration)
- Extended Spectrum: Ampicillin and its analogues, Amoxicillin. Prodrug bicampicillin, pivampicillin; talampicillin
- Other β lactam antibiotics are the carbapenems like Imipenem, meropenem, aztreonam

A brief account of the penicillins in general follows:

Mechanism of Action: Drugs belonging to this group are all bactericidal agents. They interfere with the synthesis of the bacterial cell wall.

Peptidoglycans are components of cell wall that provide mechanical rigidity and stability to the bacterial cell. The parallel glycan chain (which are polysaccharides) are cross linked by peptide chain and hence are given the name peptidoglycan. These poly- saccacharides are primarily N-acetyl glucosamine and N -acetyl muramic acid. The cross linking of these polysaccharides is called transpeptidation reaction. This step is inhibited by β lactam antibiotic and Cephalosporins.

Pencillins bind to Penicillin binding proteins associated with bacterial cell membrane. These proteins are transpeptidases and carboxypeptidases that catalyze the terminal reaction in the bacterial cell wall synthesis. This leads to the inhibition of transpeptidation reaction and consequently the peptidoglycan synthesis is blocked. Penicillins and Cephalosporin also decrease the availability of inhibitors of autolysin. The later are fact enzymes present in the bacteria. Uninhibited autolysins results in the lysis of the bacteria in an isotonic environment. Mammalian cells do not have cell wall hence, Penicillins and Cephalosporins are not toxic to the mammalian cells

Structural difference in the bacterial cell wall of Gram +ve and Gram –ve bacteria affects the susceptibility of the organism to these agents by affecting the binding and penetration of the AMA. Some penicillins can diffuse through the cell wall of gram –ve bacteria and hence show extended activity.

The AMAs are lethal in the multiplication phase of the bacteria as it is during this phase that cell wall synthesis is taking place.

Bacterial resistance: Some organisms may show intrinsic resistance to these AMAs due to :

1. Structural difference in the target enzymes
2. Inability of drugs to reach their site of action due to complex bacterial surface structure e.g., *Pseudomonas aeruginosa*.
3. The main cause of development of resistance however, is production of β lactamases which inactivates the β lactam ring structure. Bacteria which produce β lactamase include staphylococci and some strains of *E. coli*, *H influenza*, Gonococci and *Bacillus subtiles*.

To overcome this inhibition of β lactamase, clavulanic acid and sulbactam are used. This protects the AMA's from being inactivated.

4. Bacteria may modify the Penicillin Binding proteins (PBP's). The organisms which are known to develop this kind of resistance include Methicillin Resistant Staphylococcus aureus (MRSA) *Strept. pneumoniae* and Enterococcus all these microorganisms produce mutant PBPs which have low affinity to Penicillins and Cephalosporins.
5. Microorganisms may produce an efflux pumps that efficiently ejects antibiotic from the periplasma back, before the AMAs can bind to PBPs e.g., *Pseudomonas aeruginosa* and imipenem; *Salmonella typhi* and nafcillin.

Antibiotic Spectrum :

- Gram +ve Cocci : *S. pyogenes*, *S. pneumoniae*, (responsible for pharyngitis, otitis media pneumoniae), Sub-acute bacterial endocarditis, Rheumatic fever.
- Gram +ve bacilli : Clostridium sp. (organisms causing tetanus, Gas. gangrene) Listeria monocytogene (responsible for causing meningitis, listeriosis)
- Spirochetes: *Treponema pallidum* (causative organism for syphilis)
- Gram -ve Cocci : Neisseria (meningitis and gonorrhoea) Actinomycetes (abscess in Craniofacial, thoracic, abdominal regions)

Types of Penicillins :

1. Narrow spectrum penicillin : Benzyl penicillin (Pen V, Pen G) and its congeners :

- Crystalline Sod. Pen G : 100 000 units – for injection in vials of 5 doses
- Procaine Pen G : 300 000 units for injection in vials of 5 doses
- Pen G pot – Pentids tab 200 (200,000 u), 400 (400,000 u) 800 (800,000 u)
- Pen V pot : Pen V oral tab 65 mg (100,000 u)
- Pen V pot forte V: 130 mg (200,000 u)
- Benzathene Pen G (Penidure) inj. LA 6 (600,000 u), LA 12(1.2 million units), LA 24 (2.4 million unit / per vial)
- Pen GGiven I.M., I.V. 0.6 -10 million units in 4 divided doses

Crystalline penicillin and Procaine Penicillin are given in combination so as to decrease the frequency of administration and maintain blood levels for long periods

2. Anti staphylococcal Penicillin: Chiefly used for infection with β lactamase producing staphylococcal infection. These are Oxacillin, Cloxacillin, dicloxacillin nafcillin flucloxacillin and the doses are:

250 – 500 mg orally 4-6 hrs
50 – 100 mg / kg / day in children

In cases of serious systemic staphylococcal infections nafcillin 8-12 gm / day is given as an intravenous infusion administered every 2-4 hourly in equally divided doses.

Food interferes with the absorption of oral penicillins and hence they should be administered on an empty stomach or administered between meals.

3. Broad Spectrum Penicillins : Penicillins useful against both Gram +ve and gram –ve cocci and bacilli but are inactivated by β lactamases. These include Ampicillin Amoxycillin, Carbenicillin, and Ticarcillin. Pivampicillin and bacaampcillin are pro drugs of ampicillin . These drugs are effective against *Strept fecalis Hemophilus influenzae*, Enterobacteriaceae,

Dose:

Ampicillin – 500 mg orally 6 – 8 hourly
3.5 gm single dose in uncomplicated gonorrhea
300 mg/kg/day in children

Amoxicillin is better absorbed from gut

Carbenicillin is useful specifically against Pseudomonas and proteus infection e.g., burns and immune compromised patients in doses of 12 – 30 gm / day I.V. These are available as sodium salts in a dose of 4.7 meq/ g sodium which may lead to fluid retention in patients with borderline impairment of cardiac and renal function including Congestive Heart Failure.

Ticarcillin $\equiv$ Carbenicillin the dose for this drug is 1– 3 gm 6 hourly or
200 – 300 mg/ / kg/ day I.V

Ureidopenicillins include Piperacillin, Mezlocillin, azlocillin, ticarcillin. These are useful against gram –ve aerobic rods , pseudomonas.

Piperacillin is more potent than carbenicillin

Amdinocillins include Mecillinam and Temocillin. These are also called **reverse spectrum penicillin**.

Mechanism of action: They act by inhibiting the cells wall synthesis; however they act by binding to a site that is different from that of penicillins. These penicillins are effective against *E coli, Salmonella, Klebsiella, aerobacter, H. influenzae* and are used in typhoid fever, dysentery and Urinary Tract Infection

Dose : These penicillins are administered is a dose of 500 – 800 mg I.M. 6 hourly

Penicillin Units: The activity of penicillin G is defined in terms of units e.g.; Crystalline Sodium Penicillin contains 1600 units / mg or Penicillin G 1 unit = 0.6 μ g or
Pen G 600 mg = 600 million units

Most semi synthetic penicillin are used by their weights rather than units that are used for the naturally occurring penicillins

Adverse Effects : Penicillins are relatively safe drugs However, one of the most important and life threatening toxic effect of penicillin is hypersensitivity reaction. The hypersensitivity reactions may be immediate or late hypersensitivity reactions. Sensitization to penicillins is in direct proportion to the duration and total dose of penicillin received in the past. The responsible antigenic determinants are penicilloic acid, which is a metabolite of penicillin. These are several other minor determinants. Penicilloic acid combines with the host proteins which then acts as a hapten and is responsible for the allergic reaction.

Common hypersensitivity reactions include skin rashes, fever, severe, forms of hypersensitivity reactions which includes anaphylactic shock with circulatory collapse obstruction of breathing due to edema and spasm in the bronchi. Occasionally urticaria fever, joint swelling, angioneurotic edema intense pruritis, and oral lesions, intestinal nephritis may also be seen occasionally. These reactions may occur within 20 min of parenteral administration to upto 72 hrs of its administration. Treatment consists of administration of adrenaline and corticosteroids, antihistamines, O₂ inhalations

Other common side effects associated with oral penicillin include nausea, vomiting diarrhea. The incidence of diarrhea is more with ampicillin than amoxicillin. In some instances, the administration of these broad spectrum AMAs may lead to alterations in the bacterial flora of the gut which may lead to super infection with microorganism not sensitive to penicillin. The common organism found in such condition include Staphylococci, pseudomonas, proteus or yeasts.

Specific toxicity with different penicillins include:

- Oxacillin causes reversible elevation in hepatic SGOT SGPT values
- Methicillin may cause interstitial nephritis
- Carbenicillin causes reversible increase in pro-thrombin time leading to bleeding diathesis. Neuro-toxicity may also be manifested by the use of this drug
- Methicillin, nafcillin may occasionally lead to the development of granulocytopenia especially in children.

Drug Interactions: Synergistic drug interaction when penicillin is used in combination with other drugs includes the following. Penicillin used in combination with :

- a) Probenacid prolongs the action of penicillin by decreasing tubular secretion
- b) Sulbactam, clavulanic acid are β lactamase inhibitors and hence extend the spectrum of penicillins activity against β lactamase producing cocci and bacilli
- c) Given with Gentamicin penicillins acts synergistically against *Strept. Viridans Strept fecalis* in Sub Acute Bacterial Endocarditis
- d) Piperacillin and Gentamicin act synergistically in combination against Proteus and Pseudomonas infections.

Antagonistic combinations when penicillins are used with other drugs include the following:

- a) Oral penicillin antagonize the action of other bacteristatic antibiotics like tetracycline, erythromycin, chloramphenicol
- b) Penicillin and gentamicin should not be mixed in the same syringe
- c) Carbenicillin and heparin or oral anticoagulants may increase the risk of bleeding.
- d) Ampicillin in combination with allopurinol may cause non urticarial maculo-papular rash
- e) Ampicillin along with hydrocortisone in the same I.V. fluid inactivates each other

3. Other β lactam Antibiotics

Agents with β lactam ring which are neither penicillin nor Cephalosporins have been developed. These are:

a. Carbapenems : Imipenems

Mechanism of action: Like penicillin and Cephalosporins, imipenem binds to penicillin binding protein and disrupts the bacterial cell wall synthesis. However, imipenem is not hydrolyzed by β lactamases.

Antibacterial Spectrum: Gram +ve and gram -ve organism including enterobacteriaceae, Pseudomonas, N. gonorrhoea, *H. influenza*

Imipenem has to be given intravenously. It is partially metabolised in the proximal tubule and by dehydro-peptidases. Cilastatin a dehydropeptidase inhibitor when administered with imipenem leads to recovery of up to 70% of the active drug from the urine.

Adverse reactions: Adverse reactions are similar to those reported with penicillin. Patient hypersensitive to penicillin show cross hypersensitivity to imipenem.

Clinical Uses: In severe infection of Urinary Tract and Lower Respiratory tract, as also in nosocomial infection. Imipenem and Cilastatin given in a Dose of 500 mg I.V. 6 hourly have been found to be effective.

b. Aztreonam: It is a monobactam and is resistant to most β lactamases

Mechanism of Action: It binds to penicillin binding proteus and reduce the formation of filamentous bacterial structure.

Bacterial activity : Spectrum of activity includes Enterobacteriaceae, Pseudomonas aeruginosa, H influenza, gonococci

Aztreonam is administered I.M. or I.V. Patients allergic to penicillin or cephalosporins do not exhibit similar reaction to Aztreonam. It is excreted by the kidneys

Dose : Aztreonam 2 gm administered 6 -8 hourly (in patient with normal renal function). In the presence of impaired renal function the dose needs to be adjusted.

Other monobactams are Carumonam, Tigemonam, Meropenem

4. β lactam inhibitors

These drugs are structurally similar to β lactam antibiotics but they do not show any antibacterial activity. When administered along with penicillin in patient with infection due to β lactamase producing organisms they prevent the degradation of penicillin by this enzyme. These β lactams inhibitors are clavulanic acid (orally effective) sulbactam, tazobactam (administered I.M. or I.V.)

Mechanism of Action : They bind to susceptible β lactamases esp. penicillinase and prevent the hydrolysis of penicillin.

Clavulanic acid is used with amoxicillin (augmentin) and with ticarcillin (Timentin)

Sulbactam is available with ampicillin (sulbacom)

Tazobactam is combined with piperacillin and ticarcillin

5. Cephalosporins

Cephalosporins and cefamycins are naturally occurring antibiotics obtained from *cephalosporium acremonium* and *Streptomyces lactamdurans*

Chemically cephalosporins contain an active nucleus, 7 amino-cephalosporinic acid. Cephalosporins are resistant to degradation by the β lactamases present in some of the bacteria. These AMAs are active against both gram +ve and gram -ve bacteria. The chemical analogue of Cephalosporins are cefamycin which contain a dihydrothiazine ring fused to the β lactam ring present in the parent compound.

Mechanism of Action : The mechanism of action of cephalosporins is similar to Penicillins since, chemically both the AMA have a β lactam ring. They bind to the specific cephalosporin binding proteins present on the bacterial surface. Like the penicillins they inhibit the bacterial cell wall synthesis by inhibiting the transpeptidation of the peptidoglycans. These activate the autolysin enzyme present in the bacterial cell wall, resulting in the lysis of bacteria. Hence, like the penicillins, cephalosporins are also bactericidal drug.

Introduction of different side chains in the cephalosporins nucleus results in compounds with varying pharmacokinetic profile and different antibacterial activity.

Classification of cephalosporins : This is based on generations of cephalosporins which follow the chronology of their discovery e.g.; the first discovered cephalosporins are first generation, the second set of cephalosporins discovered as 2nd generation and so on.

Name	Dose Adults	pead mg/kg/d	t _{1/2} (hrs)	Metab by C'sporinase
Cephalexin	0.25-0.5g po 6hrly	25-30	0.8	Yes
Cephaoridine	same dose but route is PO IM ,IV		0.7	Yes
Cefadroxil	0.5-1g PO 12 hrly	40-60	1.5	yes
Cephazolin	0.5-2g IV 8hrly	25-100	1.5	Yes
Cefoxitin	1-2g IM, IV 6-8hrly	75-100	0.7	No
Cefuroxime	0.75-1.5g IV 8hrly	50-100	1.4	No
Cefuroxime axetil	0.25-0.5g PO 12hrly	0.125-0.25	1.4	
Cefotaxime	1-2g IV 6-12hrly	50-100 4-6hrly	0.9	No
Ceftazidime	1-2g IV 8-12 hrly	75-150 8hrly	1.8	No
Ceftriaxone	1g IV IM 24 hrly	50-100	8.5	yes

Uses

1. Treatment of severe infections caused by hemophilus influenza, klebsella, enterobacter and serratic species

2. Used as an alternative to penicillin in patients who are unable to tolerate penicillins
3. Ceftriaxone is the Drug of Choice for the treatment of all forms of gonorrhea
4. Cefoxitin and cefotaxime are effective against anaerobes
5. Third generation (except cefoperazone) are useful in the treatment of meningitis due to meningococci, pneumococci, *H.influenza*

Adverse Reactions:

1. Hypersensitivity reaction like maculopapular rash with or without fever anaphylaxis, bronchospasm, urticaria.
2. Hypothrombocytopenia and bleeding disorders. Prophylactic treatment with Vit. K 10 mg can be useful. Moxalactam has been observed to induce severe bleeding and hence is no longer used.
3. Disulfiram like reaction, have been reported with cefamandole, cefoperazone, cefotetan, moxalactam.
4. Interstitial nephritis and acute tubular necrosis have been reported with cephaloridine and cephalothin
5. Diarrhoea is observed more frequently with cefoperazone

6. Aminoglycosides

These are bactericidal antibiotics. They are derived from streptomyces (the names of these aminoglycosides ends with “mycin”) and Micromonospora (these aminoglycosides have their name ending with “micin”). They were first isolated by Waksman in 1949.

Structurally there are 2 aminosugars joined by glycosidic bond to a aminocyclitol, hence the name aminoglycoside. The aminoglycosides are highly polar drugs, they are active in alkaline pH and hence not absorbed from the gastro intestinal tract. All aminoglycosides are therefore administered parentally. They act by inhibiting the protein synthesis in the bacteria. They share common toxicity of being either nephrotoxic or ototoxic or both.

Mechanism of Action : Aminoglycosides are bactericidal agents. These AMAs penetrate the bacterial cell wall through pores present on the bacterial cell wall, by a process of passive diffusion. When aminoglycosides are administered along with penicillins there is a synergistic action. It is observed that the bacterial cell wall weakened by the action of penicillin, facilitates the diffusion of aminoglycosides.

Further transport across the cytoplasmic membrane is an active energy dependent process. Hence, aminoglycosides are ineffective against anaerobic microorganism. Aminoglycosides binds to the 30 S subunit of the ribosome of the bacteria and inhibit the protein synthesis. Aminoglycosides inhibit the protein synthesis by interfering with the formation of an initiation complex which leads to the accumulation of this abnormal initiation complex. Aminoglycoside induce the misreading of the code on the mRNA template. This results in incorrect amino acids being incorporated into the growing peptide chain. Once the initiation complex is inhibited the above process requires time for the synthesis of new ribosomes. Thus a prolonged bactericidal effect is seen even after the concentration of the aminoglycosides falls below the Minimum

inhibitory concentration (MIC) for that AMA. Hence, these drugs need to be administered only 1-2 times a day despite the short $t_{1/2}$ of these AMA.

Resistance: There are numerous mechanisms by which bacteria may develop resistance to the aminoglycosides. These include:

1. Inactivation of the aminoglycosides by enzymes like acetyl transferase, phosphotransferase and adenyl transferases present in the bacterial cells
2. The microorganisms alter their bacterial cell surface such that there is a failure of the AMAs to diffuse across the bacterial cell wall.

One of the ways to overcome this kind of resistance is to combine β lactam AMA with the aminoglycosides. The former will weaken the bacterial cell wall enabling the aminoglycosides AMA to enter the microorganism and inhibit their protein synthesis.

3. Mutation and subsequent alteration of the 30 S ribosomal sub unit thereby preventing the attachment of AMA to the ribosome.
4. Natural resistance to aminoglycosides to penetrate the cytoplasmic membranes as seen in facultative and other anaerobic bacteria.

Commonly used aminoglycosides are streptomycin, Gentamicin, Sisomicin, Netilmicin, Kanamycin, Amikacin, Neomycin, Tobramycin, Soframycin, Spectinolylin, Paromomycin

Antibacterial spectrum :

- Primarily these are active against gram -ve aerobic bacilli e.g.; *E.Coli*, *Klebsiella*, *Shigella*, *Proteus*, *Pseudomonas aeruginosa*.
- Used with penicillins they are effective against strains of streptococci and enterococci. However, their activity towards gram +ve organism is limited.

Pharmacokinetics: Aminoglycosides are poorly absorbed from the gut. Following the parenteral (I.M.) administration of the aminoglycosides, a peak concentration is achieved within 30- 90 mins. These are excreted unchanged by the kidneys. Hence, they tend to accumulate in renal insufficiency. The dose in such patients has to be adjusted according to the serum creatinine levels.

Adverse Effects: All aminoglycosides have the potential to produce ototoxicity and nephrotoxicity to varying degrees.

Gentamicin, amikacin tobramycin and neomycin have greater nephrotoxic potential. Of these, neomycin is the most nephrotoxic AMA. This effect is irreversible. In addition it is important to remember that these AMAs should not be used with drugs that cause nephrotoxicity. Use of agents like vancomycin, furosemide, cyclosporins and cisplatin may potentiate the nephrotoxic effects of aminoglycosides.

Ototoxicity can involve either vestibular or cochlear dysfunction. The vestibular and cochlear sensory cells are sensitive to the effect of aminoglycosides leading to their destruction. This effect may or may not be reversible. Streptomycin and gentamicin have greater effect on the

vestibular function whereas amikacin and kanamycin preferentially affect the auditory function. Tobramycin affects both the auditory and vestibular components equally.

The aminoglycosides have curare like activity which can cause neuromuscular junction blockade. These effects are seen more frequently in patients suffering from myasthenia gravis or in the presence of other skeletal muscle relaxing agents administered simultaneously. This effect may be reversed by administering Ca gluconate or neostigmine given intramuscularly.

Uses :

1. Tuberculosis: Streptomycin 0.75 gm IM twice weekly for 60 days. It must be given with other Anti-Tubercular drugs like Rifampicin, INH etc.
2. Tularemia: Streptomycin 1-2 gm for 7-10 days. May be administered along with tetracycline.
3. Plague Streptomycin 1-4 gm I.M. for 7-10 days.
4. Urinary tract infections: Gentamicin alone or in combination with penicillin or Cephalosporin is the treatment of choice. Gentamicin 3-5 mg/kg /day in 2-3 equal doses in adults and 2-2.5 mg/kg in children
It is important to remember that penicillins, Cephalosporin, amphotericin B and heparin should not be mixed in the same vial as this leads to *in vitro* interaction and inactivation of the amino glycosides
5. Pneumonia especially in nosocomial or hospital acquired infection patients,
6. In sepsis: Fever and Septicemia in immune-compromised patients, gentamicin is used in combination with penicillin
7. Enterococcal endocarditis -Gentamicin is given with vancomycin especially in patients allergic to penicillin
8. Meningitis due to β lactam resistant organisms: Gentamicin may be given both systemically and intrathecally; the drug may be administered simultaneously by these two routes
9. Miscellaneous -In patients undergoing peritoneal dialysis, an aminoglycoside is used locally along with the dialysis fluid in sepsis due to *Pseudomonas* infection. Gentamicin or tobramycin may be given along with an appropriate penicillin

7. Macrolide Antimicrobial Agents

These AMA contain a multimember lactone ring and hence are termed macrolide antimicrobial agents. This class includes Erythromycin, Roxithromycin, Clarithromycin, Azithromycin, Dirithromycin. Erythromycin the prototype drug is derived from *streptomyces erythreus* while the other macrolides are semi synthetic derivatives.

The antimicrobial activity of these drugs is quite similar to that of penicillins and hence, the macrolides antimicrobial agents are used in patients allergic to penicillin. Macrolides are most effective against *S. pyogenes*, *S. pneumoniae*, show moderate activity against *H. influenzae*, *N. meningitis*, *N. gonorrhea*, *Campylobacter jejuni*, *M. pneumoniae*. Atypical bacteria like *Mycobacterium scrofulaceum* and *M. Kansasii* are sensitive to erythromycin.

Mechanism of Action: Macrolides inhibit the protein synthesis in the bacteria by binding reversibly to the 50 S ribosomal subunits, thereby inhibiting the translocation of tRNA from the 'A' site i.e. from the acceptor site on the ribosome to the 'P' site the peptidyl site. This leads to inhibition of the protein synthesis.

Pharmacokinetics : Erythromycin base is destroyed by gastric acid and hence is available as enteric-coated tablets or capsules. The ester form i.e. Erythromycin stearate or ethylsuccinate or esteolate protects the base from acid degradation. The absorption of these salts is also not hindered by the presence of food.

	t_{1/2}	Adult	Children
Erythromycin	1.5 hrs	250 – 500 mg 6 hrly	5 mg / kg / day in divided doses
Roxithromycin	12 hrs.	150 mg BD	2.5 – 5 mg / kg BD
Azithromycin	68 hrs.	500 mg OD for 3 days	5-10 mg / kg / day for 3 days
Clarithromycin	6-7 hrs.	250-500 mg BD	
Spiramycin	8 hrs.	6-9 million IU/day in 2-3 divided doses for 5 day	1.5 MIU BD (6-9 yrs)

Uses:

1. In patients with streptococcal or pneumococcal infections which are known to cause pharyngitis, sinusitis, otitis media, pneumonia and respiratory infections sinusitis macrolides are used as substitutes for penicillin especially if the patients are not able to tolerate penicillins
2. It is the drug of choice for atypical pneumonia due to *Mycoplasma pneumoniae*, *Legionnaires disease pneumonia*, *Pertussis* whooping cough, *Corynebacterium diphtheria* especially in pharyngeal carriers.
3. Clarithromycin along with omeprazole and amoxicillin is used to treat *H. Pylori* infection which is associated with peptic ulcers. The treatment is given for 10 days.
4. Clarithromycin is given with ethambutol for the treatment of *Mycobacterium avium* complex in patients of AIDs
5. Prophylactic uses of erythromycin include rheumatic fever, prevention of bacterial endocarditis following dental or respiratory tract surgery. These are especially useful in patients who are unable to tolerate penicillins
6. Non-chemotherapeutic use erythromycin. This drug has anti-inflammatory activity independent of its antibacterial actions. They act by decreasing the pro-inflammatory cytokines release from the phagocytes and are thus useful in the management of rheumatoid arthritis, cystic fibrosis, asthma, chronic sinusitis etc
7. Erythromycin is used in diabetic gastro paresis as the AMA acts as a motilin receptor agonist. Motilin is a peptide of GIT and causes enhanced gastric emptying.

Adverse effects :

- Erythromycin is remarkably nontoxic. Dose related GIT symptoms include epigastric distress, abdominal cramps, nausea, vomiting.

- Cholestatic hepatitis has been reported with esteolate salt of erythromycin but rarely with the ethyl succinate or stearate salts.
- Epigastric pain due to stimulation of the motilin receptor may be seen with erythromycin. This effect is less with Azithromycin and Clarithromycin
- High doses of erythromycin may lead to transient reversible auditory impairment (hearing loss) Azithromycin in therapeutic doses could lead to the development of tinnitus.
- Administration of Erythromycin esteolate in infants, could lead to the development of hypertrophic pyloric stenosis.

Drug Interactions: Erythromycin and Clarithromycin are both inhibitors of cytochrome P450 enzyme system, which may increase the blood concentration of carbamazepine, theophylline, warfarin, cycloserine and pimozide. This drug interaction is not seen with Azithromycin as it does not effect the p450 enzyme in the liver. Administered with statins, macrolides may increase the incidence of rhabdomyolysis.

7. Miscellaneous Antimicrobials

Antimicrobial agents to be considered in this section include Vancomycin, Teicoplanin, Lincosamines like Lincomycin and Clindamycin

a. Vancomycin is obtained from *Streptococcus orientalis*. Chemically this is a tricyclic glycopeptide

Mechanism of Action : Vancomycin is a bactericidal agent. It inhibits the bacterial cell wall in susceptible bacteria by forming a complex with D-alanyl-D-alanine. which now becomes susceptible to lysis..

Antibacterial activity:Vancomycin is bactericidal to gram +ve *streptococcus*, *staph aureus*, strains resistant to nafcillin. , Gentamicin or Tobramycin when administered with Vancomycin exhibits synergistic antimicrobial activity. Other organisms susceptible to vancomycin includes *Enterococci*, *Corynebacterium diphtheria*, *Listeria*, *Clostridium tetani*, and *Bacillus anthracis*.

Pharmacokinetics: Vancomycin is poorly absorbed from GIT and hence has to be administered intravenously. Vancomycin accumulates in the body in hepatic and renal insufficiency and hence in these conditions it is important to adjust the dose. Plasma half life of vancomycin is 6 – 10 hrs.

Uses:

1. Vancomycin is primarily a second line drug for most Staphylococcal infections. It is also useful in endocarditis not responding to penicillins or Cephalosporin
2. Vancomycin is useful in infections due to MRSA and in *Staph epidermitis* infection.
Dose is 0.5 gm diluted in 200 ml of 5% dextrose or 0.9% saline and injected slowly over 60 min every 6 hrly, or 20 – 40 mg / kg/ day
3. Given orally it is useful in pseudo-membranous colitis infection due to *Clostridium difficile*

Dose:The dose of vancomycin in this condition is 125-250 mg orally every 6 hrs. The equivalent dose in infants and neonates is 15 mg / kg initially followed by 10 mg / kg 12 hourly.

Adverse drug events:

- Macular skin rashes, anaphylaxis, chills and fever have been reported.
- Intravenous infusion given rapidly could lead to “red neck” or “red man” syndrome due to the release of histamine.
- Extravasations of vancomycin during I.V. infusion could cause tissue necrosis and hence infusion should only be given in large veins.
- Vancomycin has been reported to cause both ototoxicity and renal toxicity. Vancomycin should be withdrawn if the patient develops tinnitus. Also it should be used with caution in patients concurrently receiving other ototoxic drugs like aminoglycosides.

b. Teicoplanin : Teicoplanin is a glycopeptide obtained from *Actinoplanes tiechomyetius*. It is similar in chemical structure, mechanism of action, antibacterial spectrum and clinical use to Vancomycin. Teicoplanin may be given I.M. as well as I.V. as it does not cause necrosis. It is not associated with the “red neck” syndrome as seen with vancomycin. It rarely causes nephrotoxicity. Occasional bronchospasm and hypersensitivity reactions, drug fever and neutropenia and rarely ototoxicity have been reported. Half life of Teicoplanin is 50 hrs.

c. Bacitracin : Bacitracin is a mixture of polypeptides obtained from *Bacillus subtilis*.

Mechanism Of Action : It interferes with the bacterial cell wall synthesis. It acts by interfering with the function of the carrier molecule responsible for the transfer of mucopeptide to the growing cell wall.

Pharmacokinetics : Absorption from GIT is very poor. Topical application is devoid of any significant adverse effect.

Antibacterial activity : Bacitracin is effective against *Staphylococcus aureus*, *Strept. Pyogenes*, *Clostridium*, *Neisseria*, *H.influenza*, *T. pallidum* and β lactamase producing staphylococci.

Uses : Topical application containing 500 units / g as ointment or eye drops along with neomycin and polymyxin is used for the treatment of carbuncle, pyoderma, furunculosis. It is administered orally, as an alternative to vancomycin, for the treatment of iatrogenic pseudomembranous colitis.

Dose : The dose of Bacitracin is 25,000 units 4 times a day for 7 to 14 days.

Adverse Reactions: Bacitracin is not administered systemically because of its marked nephrotoxicity. Topical application could cause skin rashes and hypersensitivity reactions.

d. Lincosamines: The first lincosamine to be used clinically was Lincomycin. However, it is now obsolete. Clindamycin is the chlorinated derivative of lincomycin and has replaced lincomycin as it has greater antibacterial activity and can be administered orally.

Mechanism of Action: Like the macrolides Clindamycin binds to the 50 S sub unit of the bacterial ribosome and inhibits the proteins synthesis. Therefore it has bacteriostatic activity.

Antibacterial spectrum: The antibacterial spectrum of Clindamycin is similar to that of erythromycin and penicillin. It exhibits its activity against streptococci, pneumococci,

staphylococci except MRSA. It is specifically effective against *Bacteroides fragilis*. Other bacteria against which Clindamycin is effective are *Pneumocystis Carinii*, *Toxoplasma gondii* and *cornyobacterium acnes*. It has shown to have same activity against chloroquine sensitive and chloroquine resistant malarial parasite *P falciparum* and *P vivax*. A cure rate of 50% has been reported with the use of Clindamycin

Pharmacokinetics: It is well absorbed orally; food does not interfere with its absorption. It is chiefly metabolized in the liver. The drug may accumulate in hepatic dysfunction where in dose adjustments may be required.

Uses:

1. Anaerobic infections: Clindamycin is primarily used in severe anaerobic infections especially due to *B. fragilis*. These organisms are known to cause lung abscess, aspiration pneumonia and oro-dental sepsis. Clindamycin is used only as an alternative to metronidazole and cephalosporins.
2. Intra-abdominal sepsis and non- sexually transmitted infections of the female genital tracts. Following septic abortion and pelvic abscess Clindamycin is indicated. It is given along with aminoglycosides.

Dose and Uses: Dose of Clindamycin is 150 – 300 mg 6 hrly and in case of severe infections 300 – 450 mg 6 hrly. Clindamycin is used with primaquine 30 mg / day x 21 days. For the treatment of *Pneumocystis carinii* in patients of AIDS it can be used as an alternative to cotrimoxazole. For toxoplasmic encephalitis in patients of AIDS, Clindamycin may be combined with pyrimethamine. The treatment is continued for 6 weeks.

Children: Clindamycin is given orally at dose levels of 30 – 60 mg / kg / day in 3-4 doses or 10 – 20 mg / kg / day parenterally in divided doses.

Adverse reactions: The most serious and sometimes fatal toxic effect seen with Clindamycin is the development of pseudomembranous colitis. This is due to the toxins liberated by *clostridium difficile* an opportunistic infection of the gut. Hence, if diarrhoea occurs following the use of Clindamycin treatment the drug should be stopped immediately. Hypersensitivity reaction, skin rashes, and urticaria can occur in 10% of the patients. Clindamycin may potentiate the effect of neuromuscular blocking agents (similar to aminoglycosides).

e. Polymyxins: Polymyxins are basic polypeptides active against gram –ve bacteria. They are extremely toxic and are not used for systemic administration. The toxicity seen on systemic administration of polymyxins is nephrotoxicity and hence, only polymyxin B + E (also known as Colistin) are used in clinically for topical applications. Polymyxins B and E are obtained from *Bacillus polymyxa* and *Bacillus colistinus* respectively

Antibacterial activity: Polymyxins act as cationic detergents. They disrupt the bacterial cell membrane leading to loss of their osmotic integrity. This leads to the leakage of intracellular constituents and subsequent death of the bacteria. Polymyxins have bactericidal action against gram –ve bacteria including *pseudomonas aeruginosa*. Polymyxins demonstrate a synergistic activity with other broad spectrum AMAs like tetracyclines and chloramphenicol.

Uses: Their use is restricted for topical applications. They are available in combination with bacitracin or neomycin, as ointment or drops for skin, eye, and ear infections. These may be injected into joints or pleural cavity or inhaled. It can also be used for its local action during bladder irrigation.

Adverse effects : If polymyxins get absorbed they may produce protenemia and hematuria and electrolyte imbalance.

Broad Spectrum Antibiotics

Tetracyclines: Tetracyclines are obtained from *Streptomyces*, *rimosus* and *Streptomyces aureofaciens* which yields chloro and oxytetracyclines. Tetracycline is a semisynthetic derivative. Structurally these Tetracyclines have four cyclic rings in their structure. The different analogues of tetracycline have the same antibacterial spectrum but differ in their pharmacokinetics properties

Commonly used Tetracyclines are :

Short acting tetracycline with a $t_{1/2}$ of 4 – 10 hours

Chlorotetracycline., oxytetracycline and tetracycline

Dose : 250 – 500 mg t.i.d. or q.i.d.

Side effects include diarrhea and varying degree of phototoxicity

Intermediate acting with $t_{1/2}$ 10 – 15 hours

Demeclocycline , Methacycline

Dose : 300 – 600 mg b.i.d.

Side effects : Diarrhoea and phototoxicity; diabetes insipidus

Long acting $t_{1/2}$ 15 – 20 hours

Doxycycline, Minocycline

Dose : 100 mg 1-2 times a day

Side effects : Phototoxicity, vestibular toxicity (minocycline).

Antibacterial spectrum: Tetracyclines are broad spectrum antimicrobial agents active against a variety of Gram +ve and Gram –ve microorganisms. In addition they are active against Rickettsiae, Mycoplasma, Chlamydia, atypical mycobacteria, amoeba; they are moderately active against *Treponema pallidum*, *Leptospira*, *Helicobacter pylori*, *Bacillus anthracis*, *Clostridium perfringens*.

Mechanism of action: Tetracyclines are primarily bacteriostatic agents and act by inhibiting the protein synthesis of the microorganism. Tetracyclines are taken up by bacteria both by passive diffusion which is through the hydrophilic channel especially in the gram negative bacteria and by an active energy dependent transport as seen in gram +ve organisms.

Once inside the cell, tetracyclines bind to the 30 S sub unit of the bacterial ribosome and thereby inhibit the elongation of the peptide chain. Mammalian cells lack the active transport system present on the bacterial cell wall and hence tetracyclines are selectively toxic to the bacterial cell.

Resistance to tetracycline: Cross resistance, is seen between the different tetracycline i.e., organism resistant to one tetracycline exhibits resistance to the other tetracycline. Resistance occurs by a decreased permeability of the drug into the bacteria or an increase in the efflux of the

tetracycline by an energy dependent mechanism. In addition there may be a decrease in the effect of tetracycline on the ribosome or like penicillins the bacteria may have enzymes that inactivate the drug.

There is a close association between the bacterial resistance to tetracyclines and to other drugs like aminoglycosides, chloramphenicol and sulfonamides. Hence an organism may show resistance to multiple drugs. For over a couple of decades the use of tetracyclines had almost reduced because of availability of better drugs..

Pharmacokinetics: Tetracyclines are incompletely though adequately absorbed from the intestines. Absorption of tetracycline is impaired by the presence of Ca^{2+} , Mg^{2+} , Al^{3+} ions contained in milk or milk products and also in antacids. These ions chelate tetracyclines and render them ineffective.

Tetracyclines are widely distributed and are stored in the reticuloendothelial cells of liver spleen and bone marrow. These AMAs also get deposited in bones and the enamel and dentine of teeth including the unerupted teeth.

Uses : Tetracyclines are drugs of first choice for the treatment of rickettsial infection (Rocky mountain spotted fever) chlamydial infection which include lymphogranuloma venereum trachoma, inclusion conjunctivitis, nonspecific urethritis and in STDs like syphilis especially when the patient is unable to tolerate penicillins. Amongst the bacterial infections tetracyclines are useful in the treatment of brucellosis, cholera, urinary tract infections, acne, tularemia and plague.

Other conditions where tetracyclines are used include amoebiasis in which condition they are administered with metronidazole. For the treatment of malaria, tetracyclines are given along with quinine or sulphadoxine, pyrimethamine combination especially in chloroquin resistant *Plasmodium falciparum* malaria.

Adverse effects: Nausea, vomiting and epigastric burning are common with tetracyclines. Administering the drug with food may minimize the GIT symptoms. Super infection in the esophagus could lead to fungal oesophagitis and in intestine *Candida albicans*, *Staph aerus* or *Clostridium difficile* overgrowth could lead to development of enterocolitis.

Bone and teeth : Tetracyclines get deposited in teeth (both deciduous and permanent teeth) leading to brownish discoloration. This is seen more commonly when tetracyclines are administered during pregnancy, in infants and young children. Tetracyclines also get deposited in the bones in children leading to suppression of their growth.

Hepatotoxicity may occur on prolonged use, or in patients with preexisting liver disease. This toxicity is also observed when tetracyclines are administered during pregnancy. Prolonged use of tetracyclines (except with doxycycline and minocycline) could result in nephrotoxicity. This is seen especially with the use of outdated and degraded tetracycline.

Photosensitization has been reported by 2% individuals treated with demeclocycline and who have been subsequently exposed to sunlight.

Contraindications: Contraindications to the use of tetracyclines include pregnancy, lactation, children below 10 years, patients with renal impairment and hepatic insufficiency. Tetracyclines should never be used after their expiry date. The use of such tetracyclines leads to a reversible form of 'fanconi syndrome'. This syndrome is characterized by nausea, vomiting, polyuria, polydipsia, proteinuria, acidosis, glycosuria, and aminoaciduria. This effect is attributed to the degradation product of tetracycline viz. epian hydro tetracycline.

Chloramphenicol : Chloramphenicol is also referred to sometimes as chloromycetin. Chloramphenicol is obtained from *Streptomyces venezuelae*. It is a unique naturally occurring AMA as it contains a nitrobenzene moiety. This nitro group may be responsible for one of the important toxicity namely aplastic anemia seen with the use of chloramphenicol.

Mechanism of Action: Like the macrolide antimicrobial agents Chloramphenicol inhibits the bacterial protein synthesis by binding reversibly to the 50 S ribosomal subunit and inhibits the peptide bond formation. It is a bacteriostatic agent except for its activity against *H. influenza* where it is a bactericidal agent.

As the mammalian mitochondria resemble the bacterial ribosome, chloramphenicol also inhibits the protein synthesis in mammalian cells. The mammalian RBC cells are especially sensitive to this drug. Chloramphenicol by binding to the 70s ribosome in eukaryotic cells may be responsible for the toxicity of this AMA.

Antimicrobial activity : Chloramphenicol is a bacteriostatic agent for many gram+ve cocci, bacilli and rickettsia. As mentioned above it is bactericidal to *H.influenza*, and some strains of *Bacteroides*. The organisms sensitive to chloramphenicol include *Salmonella typhi*, *Bordetella pertusis*. It has variable sensitivity to *E Coli*, *Klebsiella pneumoniae*, *Shigella*, *Vibrio Cholerae*, *Chlamydia* and *Mycoplasma*.

Resistance: Resistance to chloramphenicol develops as a result of production of chloramphenicol acetyl transferase by the microorganisms, which inactivates the AMA. Plasmid induced resistance may lead to multiple drug resistance including chloramphenicol, streptomycin and tetracyclines.

Pharmacokinetics : Chloramphenicol is rapidly and completely absorbed after oral administration chloramphenicol palmitate, an inactive prodrug is used as oral suspension for use in children. Chloramphenicol sodium succinate is used parenterally infections. It is widely distributed in the body tissues and fluids including the Cerebrospinal fluid.

Uses: Chloramphenicol was the drug of choice for **typhoid fever**, till resistance developed for this drug. Since Chloramphenicol is a bacteriostatic agent it does not cure the carrier state and relapses are common. However, the drug of choice for typhoid fever is cefoperazone, ciprofloxacin or ceftriaxone. Other drugs useful in typhoid fever include ampicillin, amoxicillin and cotrimoxazole.

Dose: Dose of Chloramphenicol is 500 mg q.i.d. for 3-4 days when the fever subsides followed by 250 mg q.i.d. for 7 days.

Chloramphenicol is the drug of choice for **Meningitis** due to *H. influenza* infections, as chloramphenicol is bactericidal. The usual dose is 50 – 75 mg/kg/day divided into 4 doses administered for 14 days. With the advent of 3rd generation cephalosporins such as Ceftriaxone, Cefotaxime the use of chloramphenicol has declined.

For the treatment of **serious anaerobic infections** originating in the pelvis, bowel or brain, and which is caused by *B. fragilis* and which is resistant to penicillins, chloramphenicol 2 g / day is used along with amikacin 15 mg / kg / day in lieu of metronidazole.

In patients of **Rickettsial disease** in whom tetracyclines cannot be given e.g. patients sensitive to tetracycline, or patients with renal insufficiency, and in pregnant woman, Chloramphenicol is the drug of choice.

Chloramphenicol is used as an alternative to tetracyclines for **brucellosis, cholera** and **chlamydial** infections. Chloramphenicol is used topically for treatment of eye and ear infections.

Adverse reactions: The most common toxicity with chloramphenicol is drug induced pancytopenia. This occurs due to dose related bone marrow suppression. Pancytopenia includes anemia, leucopenia, and thrombocytopenia. If detected early, these effects are reversible and cell counts return to normal on stopping the drug.

Non-dose related idiosyncratic aplastic anemia is a serious albeit rare irreversible toxicity seen with chloramphenicol. In large doses chloramphenicol may cause nausea, vomiting, diarrhea and unpleasant taste, which may last for 2-5 days. Super- infection with candidiasis may occur following a week's therapy with chloramphenicol.

Gray baby syndrome: Neonates especially premature babies do not conjugate chloramphenicol. This may lead to accumulation of the unconjugated drug in the body and inadequate renal excretion of chloramphenicol. In the neonates the symptoms starts with vomiting, refusal to suck, rapid and irregular respiration, abdominal distension and periods of cyanosis. Child develops hypothermia and turns ashen gray, ultimately there is cardiovascular collapse and death.

Drug interaction: Chloramphenicol is a potent hepatic enzyme inhibitor and inhibits the metabolism of drugs like morphine (accumulation of which causes respiratory depression) warfarin (accumulation will cause bleeding) chlorpropamide (will aggravate hypoglycemia).

Anti Tubercular Drugs (ATDs)

ATDs are mostly used for the treatment of tuberculosis, an infection caused by *Mycobacterium tuberculosis*. ATDs may be classified as :

- a) **First line drugs :** Isoniazid (INH), Rifampicin (RIF), Ethambutol (ETH), Pyrazinamide (Pza), Streptomycin (S). These drugs have greater efficacy and have acceptable toxicity.
- b) **Second line drugs:** Kanamycin, amikacin, cycloserine, capreomycin, Clarithromycin, ofloxacin, Sparfloxacin, Viomycin, Thiacetazone, Para amino salicylic acid (PAS).

These second line drug are used when there is resistance to first line drugs or when there is contraindication for the use of first line drugs. These drugs are less effective when compared to the first line drugs and are more toxic.

Tuberculosis treatment has not been very successful, resulting in the emergence of multi drug resistant tuberculosis.(MDR TB) The reason for this are many; chief among them are :

- a) Patients not completing the full course of tuberculosis treatment
- b) Presence with persistors or metabolically inactive intracellular organisms. and the chronic state of the disease
- c) Like other microorganism, mycobacterium tuberculosis develops resistance to the antitubercular drugs. The disease being a chronic infection, it becomes much more difficult to treat the disease.

To overcome some of the above factors, a combination of first line agents are used and by ensuring a good compliance to the treatment the outcome of the treatment is quite satisfactory.

First line anti tubercular drugs

a. Isoniazid (INH): Isonicotinic acid hydrazide or INH was discovered in 1945. It is still regarded as a primary and an important component of treatment of tuberculosis. Structurally it resembles pyridoxine.

Mechanism of action: It is bacteriostatic for 'resting bacilli' and bactericidal to the rapidly dividing intra cellular organism present in the macrophages as also the organism in the extracellular region. INH inhibits the synthesis of mycolic acid, an important constituent of *M.tuberculosis* bacteria. This probably explains the selective antimicrobial activity of INH.

Pharmacokinetics : Following oral administration INH is rapidly and completely absorbed from the GIT. It undergoes metabolism in the liver. N.acetyltransferase is responsible for this enzymatic degradation. In the population there is seen a genetic variation in the acetylation of INH wherein the rapid acetylators or in-activators show an average $t_{1/2}$ of INH which is $1\frac{1}{2}$ times less than that seen in slow acetylators. The average of $t_{1/2}$ of INH is 3-6 hrs.

Two important metabolites are generated following acetylation of INH. Acetylisoniazid formed may be acetylated further to either diacetyl hydrazine (non toxic metabolite) or to an acylating toxic product. This later metabolite is hepato-toxic. As part of anti-tubercular therapy when rifampicin is co-administered with INH there is a two-fold increase in the production of this hepato-toxic metabolite.

Dose: Recommended dose of INH is 5 mg / kg both in adults and in children. Under the DOT regimen (Directly Observed Therapy) wherein INH is administered 2-3 time weekly. The dose of INH in adults is 15 mg / kg and in children the dose is 10 mg / kg. Pyridoxine (Vit B6) is administered prophylactically along with INH to prevent peripheral neuropathy, an adverse effect seen with the administration of INH.

Adverse effects: It is a relatively safe drug. The two most common and important side effects of INH include peripheral neuritis (paresthesias and numbness) and hepatotoxicity. However, the

risk of fatal hepatotoxicity is very low. Pre-existing liver dysfunction, and alcohol consumption may pre dispose to hepato toxicity where as Protein energy malnutrition in children may increase the incidence of this toxicity.

Management of hepatotoxicity: Once hepatotoxicity is diagnosed on the basis of an altered AST, ALT and serum bilirubin (which should be raised by at least 2-3 times the normal values) all hepatotoxic drugs including INH, Rifampicin and pyrazinamide are stopped till the enzyme levels return to normal. This may take 2 to 3 weeks in adults and 4-5 weeks in children. Gradually the anti-tubercular drugs are reintroduced starting from half the original dose. This reintroduction of the ATD should be carried out while constantly monitoring the hepatic enzymes and looking for other evidence of hepatotoxicity. Other rare side effects include agranulocytosis, eosinophilia, thrombocytopenia, anaemia, arthritis and convulsion.

b. Rifampicin (Rifampin): It is a semi-synthetic analog of rifampicin, a macrocyclic antibiotic produced by *Streptomyces* species.

Bacterial activity : Rifampicin is active against *M.tuberculosis* and some atypical mycobacteria like *M.Kansasii*, *M. avium*, *M. Leprae*, *Staph aureus*, Meningitis, *H.influenza*, Brucella, Chlamydia and Legionella. It is bactericidal to both intracellular and extracellular mycobacteria.

Mechanism of action : The site of action for Rifampicin is the β subunit of the bacterial. DNA dependent RNA polymerase. This binding inhibits the RNA synthesis in the bacteria. The synthesis of RNA in the mammalian mitochondria requires a much higher concentration of the drug.

Resistance to Rifampicin : Resistance occurs by a single step mutation by which the drug is unable to bind to the β subunit of the RNA polymerase. Used alone, resistance to Rifampicin develops rapidly. Hence, Rifampicin is always administered along with other antitubercular drugs.

Pharmacokinetics : Rifampicin is well absorbed following oral administration. It imparts an orange color to all body fluids including saliva, urine, sputum, and tears. It is important to advise the patient about this. Rifampicin is hepatic microsomal enzyme inducer and can decrease the plasma half life of verapamil, mexiletine, theophylline, phenytoin and barbiturates, ketoconazole and cyclosporine. Rifampicin also accelerates the metabolism of estrogen and may render the oral contraceptive pills ineffective.

Dose : The usual daily dose of Rifampicin in adults and children is 10 mg /kg/ day or 600 mg daily. It is preferably given before breakfast on an empty stomach thrice a week as part of DOT regimen. The drug therapy is administered under supervision of a health care worker three times a week

Uses :

1. For the treatment of both pulmonary and extra-pulmonary tuberculosis it is administered in combination with other first line antitubercular drugs
2. For the treatment of Leprosy, Rifampicin is given in combination with dapsone

3. For the prophylaxis of meningitis due to meningococcal infection Rifampicin is given in a dose of 600 mg BD for 2 days; and for *H. influenza* meningitis the dose is 600 mg / day for 4 days.
4. For the treatment of Brucellosis, Rifampicin is given along with doxycycline
5. Rifampicin is indicated for the treatment of Osteomyelitis, and endocarditis due to MRSA infection

Adverse effects : Hepatitis is a major adverse effect. As in the case with INH, patients with history of chronic liver disease, alcoholism are at a greater risk of developing hepatitis. In children, the risk is associated with the degree of malnutrition, severity of disease, dosage and number of hepatotoxic drugs being administered simultaneously. Other adverse effects include rash, fever, nausea, and vomiting.

c. Ethambutol: Ethambutol is a tuberculostatic drug active against both typical and atypical organism including *M. tuberculosis*, *M. Kansasii*, *M. avium*.

Mechanism of action: The Mechanism of action of ethambutol is not clearly understood. It has been shown to inhibit the arabinosyl transferase enzyme and thereby it inhibits the incorporation of mycolic acid into the mycobacterial cell wall.

Resistance: Resistance to ethambutol rarely occurs especially as it is given in combination with other antitubercular drugs.

Pharmacokinetics: Ethambutol is well absorbed orally. The bioavailability of ethambutol is 80%. It is widely distributed in the body including the CSF. The $t_{1/2}$ of ethambutol is 4 hours. The half-life is prolonged in patients with renal insufficiency. The absorption is unaffected by food or antacids.

Dose : The usual adults dose is 800 – 1000 mg or 15 mg / kg / day .It is given in a dose of 1600 mg / day (30 mg / kg / day) as part of the DOT's regimen where it is administered thrice a week.. Higher doses may be required to treat tubercular meningitis.

Adverse effects: The incidence of adverse effects is less than 2%. The major adverse effects include diminished visual activity, rash, fever, gastrointestinal intolerance and hyperuricemia. Ethambutol may precipitate gouty arthritis as it decreases the renal excretion of uric acid in about 50% of patients.

Retro bulbar neuritis may develop in patients getting 25 mg / kg / day of ethambutol for more than 9 months. This leads to diminished visual acuity, central scotomata and impairment in red green color discrimination. This effect is usually reversible on withdrawing the drug. It is important to inform the patient to report any visual symptoms immediately. Periodic visual acuity testing is desirable especially in children. Ethambutol should be avoided in children less than 5 years where it may be difficult to assess visual acuity.

d. Pyrazinamide (PZA): Pyrazinamide is the pyrazine derivative of nicotinamide. It has bactericidal activity and has a specific action against *M.tuberculosis*. It is an important component of antitubercular treatment.

Mechanism of action : Mechanism of action is not definitely known. Pyrazinamide inhibits mycolic acids synthesis, an important component of bacterial cell wall. It is not effective against any other organisms as they have an efficient efflux mechanism for pyrazinoic acid and thus do not allow the accumulation of the drug within the mycobacterial cell.

Pharmacokinetics : It is well absorbed from GIT and is widely distributed in most body tissues. It has a half-life of about 9 – 10 hrs.

Dose: Daily oral dose of PZA is 1500 mg or 25 mg / kg / day. For thrice a week dosage schedule the dose is 35 mg / kg / day or 2000 mg / day.

Adverse effects: Hepatotoxicity is a common and major adverse effect with PZA. It is therefore important to monitor liver function tests frequently. PZA should be avoided in patients with pre-existing liver disease or in chronic alcoholics. PZA decreases the tubercular excretion of uric acid resulting in hyperuricaemia and acute arthritis. Nausea, vomiting and photosensitivity are other rare side effects. PZA should be avoided during pregnancy.

e. Streptomycin (SM)

Antitubercular activity: Streptomycin is active against *M.tuberculosis* and also against the atypical *Mycobacterium Kansasii* and *M.avium intracellulare*. SM is less effective than INH and Rifampicin. This drug has to be administered intramuscularly. Resistance develops rapidly if used alone. $t_{1/2}$ in blood is 2-3 hrs.

Dose : The dose of streptomycin is 0.75mg to 1g IM, or 15mg/Kg/day. The dose is reduced to 500-750mg in elderly and in patients with renal dysfunction.

Adverse effects: The chief adverse effect with SM is ototoxicity and is manifested as vertigo and hearing impairment. Ototoxicity may be more severe when SM is administered with other ototoxic agents. Renal toxicity may occur with greater frequency in patients with renal insufficiency.

Uses: SM is a reserve first line drug. It is used in TB meningitis, bone tuberculosis and miliary tuberculosis. It also finds usefulness in patients with drug-induced hepatotoxicity when it is administered along with ethambutol.

Second Line Antitubercular Drugs

The second line antitubercular drugs are indicated in patients who have infection resistant to first line drugs.

a. Kanamycin and Amikacin : These are aminoglycosides antimicrobial agents. Kanamycin is obsolete. Amikacin is a less toxic alternative. Amikacin is also used in multidrug-resistant (MDR) tuberculosis. Amikacin is also useful for the treatment of disseminated *M.avium* complex in patients of AIDS

Dose: The dose of Kanamycin is 15 mg / kg/day I.M. or I.V. and that of Amikacin is 7.5 mg/kg/day I.M. administered for 5 days a week for 2 months followed by 1 g / day thrice weekly for another 4 months. Ototoxicity and nephrotoxicity are common side effects. These drugs should **not** be used along with streptomycin.

b. Cycloserine: Cycloserine is a chemical analog of the amino acid d-alanine. It inhibits the bacterial cell wall synthesis.

Antibacterial activity: Cycloserine has tuberculostatic activity against *M. tuberculosis*. It is also effective against *E.coli*, *Staph. aureus*, *Enterococcus*, *Nocardia*, *Chlamydia*.

Pharmacokinetics: It is effectively absorbed following oral administration and widely distributed in body fluids including the CSF. It is excreted in the urine.

Dose: Cycloserine is administered in a dose of 20 – 30 mg/kg/day in 2 divided doses up to a maximum of 1 gm / day.

Use: It is useful in the treatment of TB meningitis, renal tuberculosis and for the management of multi drug resistant (MDR) tuberculosis.

Adverse effects: The adverse effects are primarily attributed to the CNS and include headache, dizziness, tremors, dysarthria, visual disturbance and psychotic behavioral disorders. The effects are generally reversible. The drug is therefore, contraindicated in epileptic patients and in psychiatric patients.

b. Capreomycin : Capreomycin is a cyclic peptide used for resistant cases or in patients with treatment failure. It is administered in combination with INH and ethambutol.

Antibacterial activity: It is effective against *M. Tuberculosis*, *M. Kansasii* and *M. avium*.

Pharmacokinetics: It is poorly absorbed from GIT and hence has to be used parenterally.

Dose: Capreomycin is given in a dose of 15-30 mg/kg with a maximum of 1 g / day IM given 2-3 times a week for 2-4 months.

Adverse effects : The **adverse effects** are attributed to the 8th cranial nerve dysfunction wherein both vestibular and hearing components are involved. Renal toxicity is more common with capreomycin than seen with streptomycin. It is advisable to monitor the auditory and renal functions periodically.

c. Thiacetazone : It is a tuberculostatic agent. Because of its low cost it is used in combination with INH in many developing countries.

Dose: Thiacetazone is administered in a dose of 150 mg (2.0 mg/kg) daily orally

Adverse effects : The adverse effects include ototoxicity and hypersensitivity reactions. These include hepatitis, bone marrow depression aplasia, neutropenia, and thrombocytopenia.

d. Para Amino Salicylic acid (PAS): This is a structural analogue of Para Amino Benzoic Acid (PABA). It resembles sulfonamides and acts as an antimetabolite for *M tuberculosis* inhibiting the synthesis of folic acid in the bacterial cell. It has bacteriostatic activity. It is well absorbed orally and is distributed in all body fluids. The concentration of PAS is high in the urine, which results in the drug crystallizing in the urine leading to the development of crystalluria

Dose : The dose of PAS for the treatment of Tuberculosis is 150 mg / kg/day or 8-12 g / day orally in 2-3 divided doses administered after food to avoid gastric acidity.

Adverse effects: Adverse effects include severe GIT intolerance (anorexia, nausea, epigastric pain and diarrhea that may necessitate stopping the drug. Hypersensitivity reaction includes fever, skin rash, joint pain and hepatitis.

e. Ethionamide: Ethionamide is a tuberculostatic drug. It is a derivative of thioisonicotinamide. It is active against both the intracellular and extra cellular *M .tuberculosis* including the atypical organism. It is well absorbed orally and given in a maximum dose of 1 g / day which may cause severe GI side effects. It is rarely used now.

Newer antitubercular drugs

With the advent of Multi drug resistant (MDR) tuberculosis and the association of complex infections with AIDS it is imperative that new drugs and strategies are developed for the treatment of TB in these situations. However, thus far, none of the newer regimens or drugs have proved to be as effective as the first line drugs mentioned above.

a. Rifapentine : Rifapentine an analogue of Rifampicin has the same mechanism of action, clinical profile and adverse effects and cross-resistance as that of the parent drug.. The chief points of difference from Rifampicin is in the fact that rifapentine has a longer life, it has better bioavailability and better tissue penetration and induces hepatic microsomal enzymes to a lesser extent and hence has fewer drug interaction.

b. Rifabutin or Mycobutin : Rifabutin is also an analogue of rifampicin. Like Rifapentine its mechanism of action, spectrum of antibacterial activity and adverse effects is similar to that of Rifampicin. However, in addition Rifabutin has a better activity than Rifampicin against *M .avium* complex; some resistant strains *M. fortuitum* and *M. leprae*. Like rifapentin its induction of microsomal enzymes is to a lesser extent and hence has fewer drug interactions.

Dose : Dose of Rifabutin is 300mg/day (5mg/kg/day) and administered orally

Uses: In the treatment of *M avium* complex infection in patients of AIDS

Adverse effects: It colors the urine and other body fluids red-orange. Uveitis and arthralgias have been reported especially if Rifabutin is used in higher doses.

c. Fluoroquinolones: Fluoroquinolones have been tried in patients with multi drug resistant tuberculosis and in the treatment of atypical mycobacterial infections in patients of AIDS

d. Ciprofloxacin, is administered in a dose of 750mg two times a day or 500mg three times a day. It can be used along with amikacin, Clarithromycin, Rifampicin, ethambutol and clofazamine in the treatment of atypical mycobacterium infections.

e. Ofloxacin given in a dose of 300-400mg twice a day orally for 6-8 weeks can be given with INH, Pyrazinamide, cycloserine, ethionamide and kanamycin for the treatment of resistant cases of *Mycobacterium tuberculosis*. Higher doses of ofloxacin for a biweekly regimen is being tried.

f.Ciprofloxacin and amikacin have been tried for the treatment of atypical mycobacterial infections like *M. Kansasii* and *M. fortuitum*.

Other fluoroquinolones being tried include Sparfloxacin, Moxifloxacin and levofloxacin

Macrolides: Newer macrolides antibacterial agents like Roxithromycin, azithromycin and Clarithromycin are being tried with promising results. These macrolides have to be given in combination with other drugs to prevent the development of resistance. Clarithromycin 500-1000mg is administered twice a day. Azithromycin, 500mg daily is given with ethambutol, rifampicin, rifabutin

Treatment of Tuberculosis

In spite of effective drugs available for the treatment of tuberculosis (TB) there exists a problem of emergence of resistant bacteria and recurrence of the infection. The reason for this may be multiple. The treatment of tuberculosis requires prolonged duration of treatment schedules, which leads to poor compliance by the patient. This may be compounded by the rapid development of drug resistance, drug toxicity and emergence of higher risk category of patients; e.g., patients in whom Tuberculosis is associated with AIDS, diabetes etc.

The National Tuberculosis program has provided guidelines for the treatment of TB. This is based on the recommendations of The World Health Organization (WHO). Directly Observed Treatment Strategy (DOTS) has been devised to ensure that the anti-tubercular drugs are administered under the direct supervision of the health care workers for three days in a week. This ensures a better patient compliance and a decrease in the incidence of development of drug resistant TB infection.

Five drugs are currently recommended as essential for treatment of TB. These include INH, Rifampicin (RMP), Pyrazinamide (PZA), Streptomycin (SM), and Ethambutol (ETB).

The treatment regimen is divided into two phases: an initial intensive phase lasting for 2-3 months followed by a continuous phase for 4-6 months. Table I gives the guidelines of the recommended schedule for the different categories of Tuberculosis.

Table I: WHO Categorization of Patients and Recommended Dose Regimens

Category and Type of Patient	Duration of Treatment	Drug Regimen*
Category I - New (untreated) smear positive pulmonary TB - New (untreated) smear negative pulmonary TB <i>but seriously ill</i> - New cases of seriously ill extra pulmonary TB	For all such cases Intensive phase (2 months) followed by: Continuation phase (4 months) Total 6 months	INH + RMP + PZA+ ETB INH + RMP
Category II Smear positive re treatment group due to : - Treatment failure - Relapse / default	For all such cases Intensive phase (2+1=3months) followed by : Continuation phase (5 months) Total 8 months	2 months : INH + RMP + PZA + ETB + SM 1 month : INH + RMP + PZA + ETB INH + RMP + ETB
Category III - New (untreated) smear negative pulmonary TB but not seriously ill - Less severe cases of extrapulmonary TB	For all such cases Intensive phase (2 months) followed by : Continuation phase (4 months) Total 6 months	INH + RMP + PZA INH + RMP

* All drugs are given thrice weekly under DOT scheme.

INH – Isoniazid; RMP – Rifampicin; PZA – Pyrazinamide; ETB – Ethambutol; SM – Streptomycin

Multi drug resistance (MDR) poses a great problem and is a challenge in anti-tubercular therapy. Resistant to antitubercular drugs may be:

- Primary resistance – where in a patient is infected by a strain of *M. tuberculosis* which is resistant to one or more drugs
- Secondary resistance: Where in a mutant resistant strain *M. tuberculosis* during the course of antitubercular treatment develops as a dominant population.

Resistant may develop to INH or INH and RMP or to many other drugs. These cases are difficult to treat and may prove to be fatal. The association of AIDS, Diabetes etc. in these patients, may further compound this.

The treatment in such patients should aim at administering drugs to which the organism is sensitive to e.g.

- INH resistant cases may be treated with RMP + PZA+ETB for 12 months.
- For RMP resistance, INH + PZA + ETB is administered for 12 months

- For INH + RMP resistance, PZA + ETAB + SM (or Ethionamide + Ciprofloxacin or Ofloxacin or Levofloxacin) is given for 12 - 18 months.

Chemoprophylaxis: is indicated in:

- a) Children exposed to Sputum positive adult patients.
- b) Patients with immune compromised status like HIV / AIDS, children with positive tuberculosis test with vague symptoms of fever cough, not responding to standard treatment.
- c) Asymptomatic tubercular positive children below 12 years with a positive family history
- d) Neonates born to mother suffering from tuberculosis.

The **regimen** that are followed for chemoprophylaxis of tuberculosis are:

- INH 300mg/day (5 mg / kg/day for children) for 6-12 months
- INH 5 mg / kg/day + Rifampicin 10 mg/kg/day for a period of 6 months

Role of Corticosteroids: Normally corticosteroids are not indicated for the treatment of TB except in special circumstance such as:

- a) Seriously ill patients with miliary tuberculosis associated with respiratory distress.
- b) To prevent adhesions in patients with TB meningitis, TB pericarditis, pleural effusion or renal tuberculosis.
- c) In seriously ill patient with AIDS
- d) As replacement therapy in tuberculosis induced adreno-cortical insufficiency

Tuberculosis, pregnancy and breast-feeding

INH, RMP, PZM and ETB (during last trimester only) are all safe to be given in pregnancy. Full antitubercular treatment is advocated for lactating women; however, infants whose mothers are suffering from TB should receive INH chemoprophylaxis.

Drug Treatment of Leprosy

Leprosy is chronic granulomatous infection caused by acid-fast bacilli *Mycobacterium leprae*. The disease mainly manifests with lesions on the skin, mucous membrane and the nerves.

Indian leprosy association has classified leprosy on the basis of clinico- pathological characteristics:

- a) Indeterminate type: Patient has definite sensory impairment with one or more hypo-pigmented macules.
- b) Tuberculoid type: with one or two well-defined lesions, which may be flat or raised, hypo-pigmented or erythematous patches, which are anesthetic. The lesions are bacteriologically negative.
- c) Borderline type: 4 or more lesions flat or raised, ill defined hypo pigmented or erythematous, with sensory impairment. This normally progresses to the lepromatous type if left untreated.

- d) Lepromatous type: Diffuse infiltration or numerous flat or raised poorly defined, shiny, smooth, symmetrically distributed lesions. These are bacteriologically positive.
- e) Pure neuritic type: wherein nerve involvement is seen and there are no lesions on the skin. They are bacteriologically negative.

Like for any other condition the aim of the treatment is to achieve bacteriological and clinical cure. However, it is also important to treat the psychological, environmental and physical deformities associated with this disease.

Drugs found useful for the treatment of leprosy include :

Sulfones:	Dapsone, Sulfoxone , Ace dapsone
Phenazine derivative :	Clofazamine
Antituberculosis drug :	Rifampicin
Sedative hypnotic :	Thalidomide
Antimicrobial agents :	Ofloxacin, Sparfloxacin, Clarithromycin, Minocycline

Dapsone and other Sulfones :Dapsone also referred to as DDS or diamino-diphenyl sulfone. It is most widely used for the treatment of leprosy and remains the drug of choice in spite of development of large number of other sulfones.

Mechanism of action: Sulfones have leprotstatic activity and inhibit the bacterial folic acid synthesis, by inhibiting the incorporation of PABA into folic acid. The specificity of action of this drug may indicate a special affinity to the folate synthetase of *M. leprae* microorganism.

Resistance : Resistance of *M. Leprae* to dapsone may be:

Primary	Resistant organisms may be acquired from a patient harboring resistant bacilli.in a newly infected patients.
Secondary	Resistance to sulfone develops while the patient is being treated with a single drug .

Therefore, it is recommended that a combination of dapsone be used with Rifampicin and clofazamine.

Pharmacokinetics : Dapsone is slowly but completely absorbed after oral administration and is distributed through out the body fluids and tissues. Skin, muscle, liver and kidney retain a high concentration of the drug for upto 3 weeks of stopping the treatment. It undergoes entero- hepatic circulation. It is metabolized by acetylation in a manner similar to INH. Plasma half life is 1-2 days.

Uses:

- 1) Leprosy in combination with other drugs
- 2) Malaria resistant to chloroquine
- 3) In patients of AIDS with *pneumocystis carinii* infection

Dose

- 1) Dapsone is administered in a dose of 100 mg / day for 3-5 years (1-2 mg / kg in children)
Acedapsone is a pro-drug and is administered I.M. It has a $t_{1/2}$ of 46 days.
A single dose provides an inhibitory concentration for upto 3 months.
- 2) Malaria : Dapsone is used with pyrimethamine in chloroquin resistant malaria.
- 3.) Pneumocystitis carinii : for treatment and its prevention in patients with AIDS
100 mg / day prophylaxis; and along with trimethoprim 15 – 20 mg/kg/day for 21 days along with 100 mg dapsone, for treatment of this infection.

Adverse effects : Dapsone is generally non toxic and well tolerated agent. Mild symptoms includes intolerance occurring initially but which later subsides

Lepra reaction: During the therapy for lepromatous leprosy, patients may develop **Type I** Lepra reaction, which is primarily a delayed type of hypersensitivity reaction. This is characterized by cutaneous ulceration and multiple nerve involvement. Prompt treatment with corticosteroids is recommended to prevent nerve damage. **Type 2-lepra** reactions known as Erythema nodosum leprosum (ENL) represents a humoral antibody response to the dead bacteria. This is characterized by an abrupt onset, existing lesions enlarge and became red and inflamed and painful. Administration of corticosteroids, clofazamine or thalidomide controls and checks the reaction. ENL may sometimes be difficult to distinguish it from the normal progression of the underlying disease.

Other effects include hemolysis, and methhemoglobinemia in patients with G6PD deficiency. Skin sensitization may occur in dark skinned patients. Milder effects include loss of appetite, nausea, pruritis, drug fever, reversible neuropathy and hepatotoxicity.

Rifampicin : Rifampicin is the only drug that rapidly renders the leprosy patients non-contagious. It is a bactericidal agent and is able to destroy over 99% of the bacilli in 3-7 days following a single oral dose of 600 – 1500 mg. However, the treatment of leprosy requires prolonged treatment and during this time the bacteria are known to develop resistance rapidly. Hence, WHO recommends that the drug always be given in combination with other anti-leprosy agents. Rifampicin is effective even when administered at monthly interval.

Dose : Rifampicin is given in a dose of 600 – 900 mg once a month given along with other anti-leprosy drugs. This reduces the chance of enzyme induction, minimizes development of hepatotoxicity.

Clofazamine: Clofazamine is a phenazine dye that has both anti-leprosy and anti- inflammatory activity.

Mechanism of action : It is a week bactericidal against *M.Leprae* and preferentially binds to the mycobacterial DNA thereby inhibiting the template function of DNA.

Pharmacokinetics: Oral absorption is variable and incomplete. It is distributed widely, including the phagocytes and is stored in the reticulo- endothelial cells from where it is released slowly.

Use : In patients of leprosy, who are intolerant or resistant to dapsone. Treatment with clofazamine reverses the intolerance making the patient receptive to dapsone once again. It is useful in preventing the development of erythema nodosum leprosum (ENL). Like Rifampicin clofazamine acts intracellularly.

Dose: Clofazamine is given in a dose of 100 mg / day orally

Adverse effect : The most prominent and disturbing adverse effect of clofazamine is the red – brown discoloration of skin, mucous membrane, urine and sweat. This may be distressing in fair skinned patients. It may discolor the conjunctiva and produce photo-toxicity. Patient may experience abdominal pain due to the deposition of clofazamine crystals in the intestinal mucosae.

There is biological lag of 6-7 weeks before, the action of the drug is manifested and hence it is important to administer clofazamine as part of multi drug regimen therapy

Alternative drugs useful in the treatment of leprosy include :

Fluroquinolones :

- Ofloxacin - 400 mg / day
- Pefloxacin - 400 mg BD
- Sparfloxacin - 400 mg OD as followed by 200 mg /days
- Clarithromycin - 500 mg / day
- Minocycline - 100 mg /day

Thalidomide: A sedative hypnotic which fell to disrepute because of its association with congenital malformation (phocomelia) when administered to pregnant women. However, thalidomide is effective in the treatment of erythema nodosum leprosum (ENL).

Dose: Thalidomide is given to patients in a dose of 100 – 300 mg / day. Its use is limited and is not available freely in the market.

Treatment of Leprosy : Leprosy being a chronic infective condition is difficult to treat because of the tendency of bacilli to develop resistance, and due to the presence of metabolically inactive forms of bacilli called persisters present in the body. Hence, the chief objective of therapy in leprosy is:

- a) To render the patient non-infective at the earliest stage so as to interrupt the transmission of infection in the community.
- b) To prevent or inhibit the growth and multiplication of the bacilli in the patients
- c) To prevent the development of resistance organisms
- d) To control lepra reaction

Multi drug therapy as in the case of tubercular treatment is cost effective and helps to improve patient compliance.

Doses: The WHO recommended doses of drug for the treatment of leprosy are:

Dapsone - 100 mg daily self-administered

Rifampicin - 600 mg once a month under supervision

Clofazamine - 300 mg once month supervised and 50 mg daily self administered.

Treatment of **Paucibacillary** (Tuberculoid) smear negative active cases:

Dapsone 100 mg daily and Rifampicin 600 mg once a month supervised for 6 months. After this dapsone is continued at 100 mg / day dose even if patient shows signs of activity. However, if dapsone is not tolerated, clofazamine 50 mg daily and 300 mg once a month may be substituted.

For **multibacillary** (lepromatous) cases with smear positive:

Dapsone 100 mg daily for 2 years and Rifampicin 600 mg daily for two weeks followed by 600 mg once a month along with Clofazamine 100 mg on alternative days or 50 mg daily for 2 years.

Chemoprophylaxis

Dapsone 1 – 4 mg / kg / week is given as protection to children who are in contact with leprosy patient. This is given for 3 years or till the index case in each household becomes negative. This prophylactic effect can last up to 8 years.