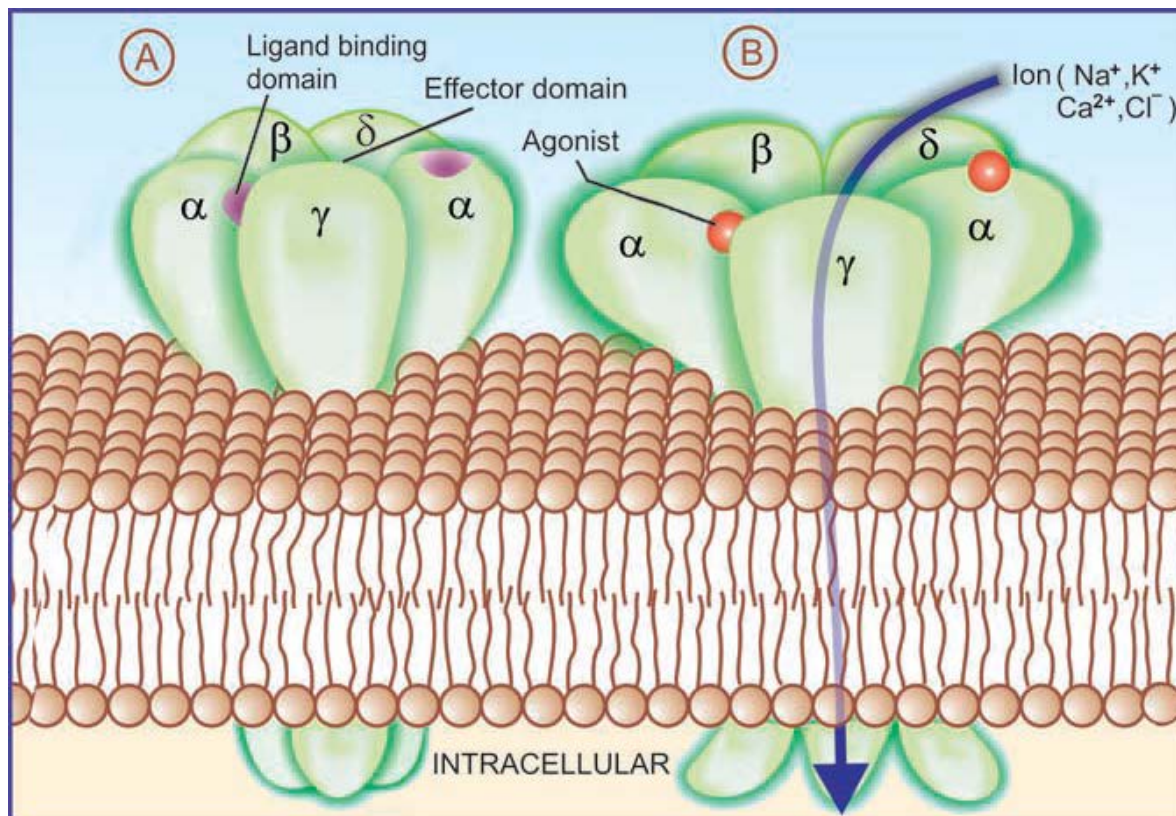


# Pharmacology



(Adopted from KD Tripathi Book)

<b>SUBJECT</b>	<b>Pharmacology-III</b>
<b>PROGRAMME/COURSE</b>	<b>Pharmacy/B. Pharmacy</b>
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## UNIT II: 3. Chemotherapy

(General Principles of Chemotherapy, Sulfonamide and Antibiotics)

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### Introduction

There are so many microorganism are exist in the universe which are responsible for causing various diseases. Therefore, it is very important to know about their characteristics and disease causing by them so that effective treatment can be provided. **Microorganisms or microbes are those tiny living things which can't be seen by naked eye.**

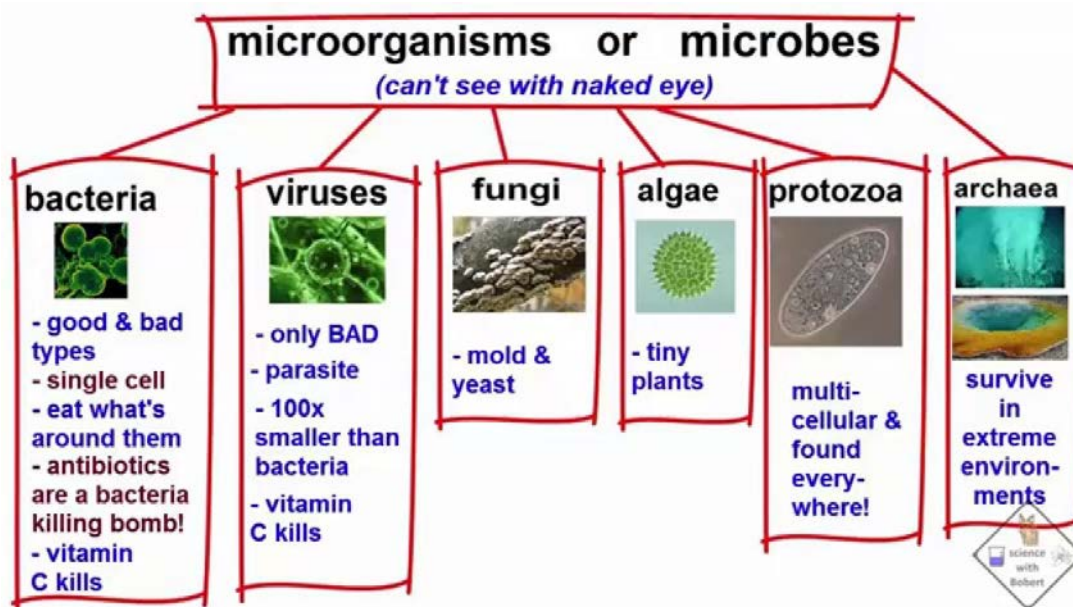


Figure 1: Different types of microbe

Table 1: Common Microbial Diseases

<b>Infectious disease</b>	<b>Microbe that causes the disease</b>	<b>Type of microbe</b>
<b>Chickenpox</b>	<i>Varicella zoster</i>	<b>Virus</b>
<b>Whooping cough</b>	<i>Bordatella pertussis</i>	<b>Bacterium</b>
<b>TB (Tuberculosis)</b>	<i>Mycobacterium tuberculosis</i>	<b>Bacterium</b>
<b>Malaria</b>	<i>Plasmodium falciparum</i>	<b>Protozoan</b>
<b>Ringworm</b>	<i>Trichophyton rubrum</i>	<b>Fungus</b>
<b>Athletes' foot</b>	<i>Trichophyton mentagrophytes</i>	<b>Fungus</b>

- Antimicrobial drugs are the greatest contribution of the 20th century to therapeutics.
- These drugs have both palliative (mitigation) and curative effect on disease.
- These play significant role in developing countries like India where infective disease are predominate.
- These are most frequently used as well as misused drugs.

## Definitions

**Antimicrobial agent (AMA)** – These includes synthetic as well as naturally obtained drugs that attenuate microorganisms. e.g. Sulfonamides

**Chemotherapy** – It is the treatment of systemic infections with specific drugs that selectively suppress the infecting microorganism without significantly affecting the host. e.g. Antimalarial drugs

**Antibiotics** – These are the substances produced by microorganisms, which selectively suppress the growth of or kill other microorganisms at very low concentrations. e.g. Penicillins

- This definition excludes **other natural substances which also inhibit microorganisms but are produced by higher forms (e.g. antibodies)** OR
- even those produced by microbes but are **needed in high concentrations (ethanol, lactic acid, H<sub>2</sub>O<sub>2</sub>)**.

✚ More specifically term antimicrobial agents (AMAs) is used instead of chemotherapeutic agents

## History of Chemotherapy

### Divided 3 phases

- (a) The period of empirical use (16<sup>th</sup> to 17<sup>th</sup> Century)
- (b) Ehrlich's phase of dyes and organometallic compounds (1890–1935)
- (c) The modern era of chemotherapy (1935 to till date)

#### (a) The period of empirical use (16<sup>th</sup> to 17<sup>th</sup> Century):

- Use of 'mouldycurd' by Chinese on boils,
- Chaulmoogra oil by the Hindus in leprosy,
- Chenopodium by Aztecs for intestinal worms,
- Mercury by Paracelsus (16<sup>th</sup> Century) for syphilis,
- Cinchona bark (17<sup>th</sup> Century) for fevers.

#### (b) Ehrlich's phase of dyes and organometallic compounds (1890–1935):

- Given an idea that dyes can selectively produce toxic effect on microbes
- He tried methylene blue, trypan red, etc.
- He developed the arsenicals—atoxyl for sleeping sickness, arsphenamine in 1906 and neoarsphenamine in 1909 for syphilis.
- **Paul Ehrlich coined the term 'chemotherapy' (bcz he used drugs of known chemical structure)**

#### (c) The modern era of chemotherapy (1935 to till date)

- **1935 (Domagk) - Prontosil (sulfonamide dye) in Pyogenic infection**
- **1938 - Sulfapyridine (M & B 693) - first marketed sulfonamide**

## Development of Antibiotics

- 🚩 **1877 (Pasteur):** growth of anthrax bacilli in urine was inhibited by air-borne bacteria
- 🚩 **1929 (Fleming):** found that a diffusible substance (Penicillin) was elaborated by Penicillium mould which could destroy Staphylococcus on the culture plate
- 🚩 **1941 (Chain and Florey):** clinical use of penicillin for wounds during second world war

- ✚ **1944 (Waksman and his colleagues):** discovered streptomycin from Actinomycetes (soil microbes) - **Treasure-house of antibiotics**
- ✚ **Sooner tetracyclines, chloramphenicol, erythromycin were developed.**
- ✚ **Development of Semisynthetic & novel synthetic AMAs, e.g. fluoroquinolones, oxazolidinones.**

## Classification of Antimicrobial agents (AMAs)

AMAs can be divided into 6 types based on following aspects:

- A. Chemical Structure**
- B. Mechanism of action**
- C. Type of organisms against which primarily active**
- D. Spectrum of activity**
- E. Type of action**
- F. Source of origin**

### **A. Based on Chemical Structure**

#### **1. Sulfonamides and related drugs:**

Sulfadiazine and others,  
Sulfones—Dapsone (DDS),  
Paraaminosalicylic acid (PAS)

#### **2. Diaminopyrimidines:**

Trimethoprim  
Pyrimethamine

#### **3. Quinolones:**

Nalidixic acid  
Norfloxacin  
Ciprofloxacin  
Prulifloxacin

#### **4. $\beta$ -Lactam antibiotics (PCTM):**

Penicillins  
Cephalosporins,

Monobactams

Carbapenems

**5. Tetracyclines:**

Oxytetracycline

Doxycycline

**6. Nitrobenzene derivative:**

Chloramphenicol

**7. Aminoglycosides:**

Streptomycin

Gentamicin

Amikacin

Neomycin

**8. Macrolide antibiotics:**

Erythromycin

Clarithromycin

Azithromycin

**9. Lincosamide antibiotics:**

Lincomycin

Clindamycin

**10. Glycopeptide antibiotics:**

Vancomycin

Teicoplanin

**11. Oxazolidinone:**

Linezolid

**12. Polypeptide antibiotics:**

Polymyxin-B

Colistin

Bacitracin

Tyrothricin

**13. Nitrofurantoin derivatives:**

Nitrofurantoin

Furazolidone

**14. Nitroimidazoles:**

Metronidazole

Tinidazole

**15. Nicotinic acid derivatives:**

Isoniazid

Pyrazinamide

Ethionamide

**16. Polyene antibiotics:**

Nystatin

Amphotericin-B

Hamycin

**17. Azole derivatives:**

Miconazole

Clotrimazole

Ketoconazole

Fluconazole

**18. Others:**

Rifampin

Sod. fusidate

Cycloserine

Viomycin

Ethambutol

Thiacetazone

Clofazimine

Griseofulvin

**B. Based on Mechanism of Action (MAO)**

**1. Inhibit cell wall synthesis:**

Penicillins

Cephalosporins

Cycloserine

Vancomycin

Bacitracin

**2. Cause leakage from cell membranes:**

**Polypeptides**—Polymyxins, Colistin, Bacitracin

**Polyenes**—Amphotericin B, Nystatin, Hamycin

**3. Inhibit protein synthesis:**

Tetracyclines

Chloramphenicol

Erythromycin

Clindamycin

Linezolid

**4. Cause misreading of m-RNA code & affect permeability:**

**Aminoglycosides**—Streptomycin, Gentamicin, etc.

**5. Inhibit DNA gyrase:** Fluoroquinolones—Ciprofloxacin & others.

**6. Interfere with DNA function:** Rifampin

**7. Interfere with DNA synthesis:** Acyclovir, Zidovudine

**8. Interfere with intermediary metabolism:**

Sulfonamides, Sulfones, PAS, Trimethoprim, Pyrimethamine, Metronidazole

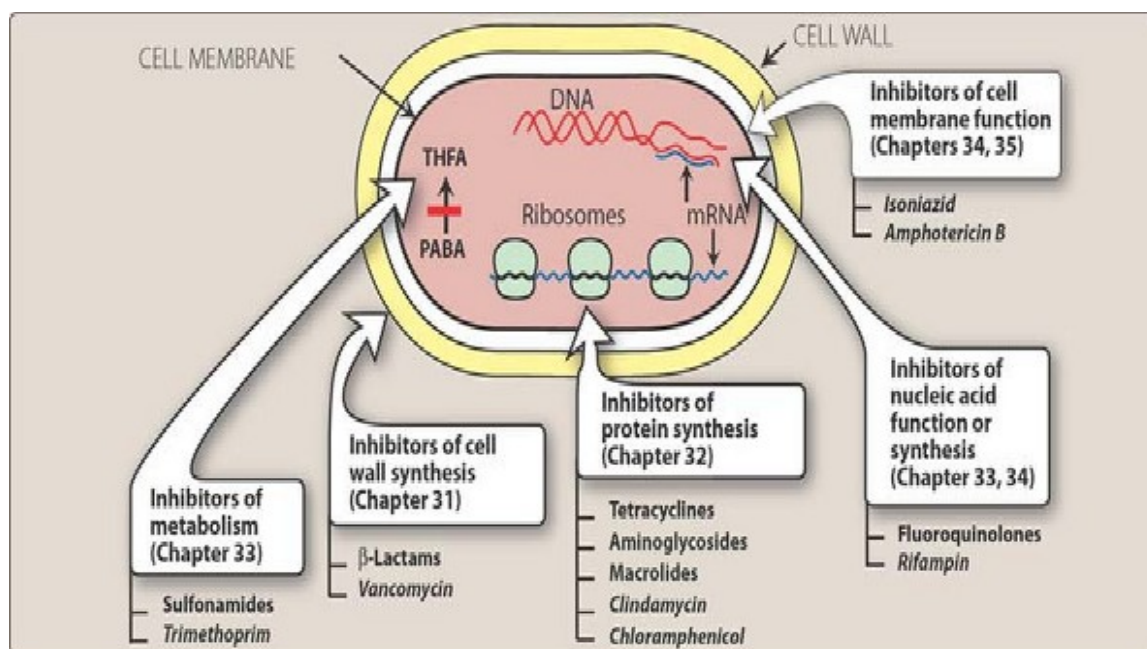


Figure : Mechanism of Action of different Antibiotics (adopted from Lippincott)

**C. Based on Type of organisms against which primarily active**

- 1. Antibacterial:** Penicillins, Aminoglycosides, Erythromycin, Fluoroquinolones, etc.
- 2. Antifungal:** Griseofulvin, Amphotericin B, Ketoconazole, etc.
- 3. Antiviral:** Acyclovir, Amantadine, Zidovudine, etc.
- 4. Antiprotozoal:** Chloroquine, Pyrimethamine, Metronidazole, Diloxanide, etc.
- 5. Anthelmintic:** Mebendazole, Pyrantel, Niclosamide, Diethyl carbamazine, etc.

**D. Based on Spectrum of Activity**

<b>Narrow</b> (agent acting only on a single or limited group of microorganism )	<b>Extended</b> (effective against gram +ve & few gram-ve bacteria)	<b>Broad</b> (effective against wide range of microbes)
Penicillin G & V	Aminoglycosides	Tetracyclines
Penicillinase-resistant penicillins (cloxacillin, dicloxacillin)	Carbacephems	Chloramphenicol
Bacitracin	Cephalosporins	Sulfonamides
Clindamycin	Extended spectrum of penicillins (Ampicillin, Amoxicillin)	Trimethoprim
Macrolides	Fluoroquinolones	Amoxicillin plus clavulanic acid
Metronidazole, Polymyxin, Vancomycin		

**E. Type of action****Bacteriocidal**(Kills bacteria - **Irreversible**)**Bacteriocidal antibiotics:**  
remember of "BANG Q R.I.P."**B**eta-lactams**A**minoglycosides**N**itroimidazoles (metronidazole)**G**lycopeptides (vancomycin)**Q**uinolones**R**ifampicin**P**olymyxins (colistin)**Bacteriostatic**(Inhibits growth of bacteria and replication- **Reversible**)**Bacteriostatic antibiotics:**  
remember of "Ms. Colt"**M**acrolides**S**ulfonamides**C**hloramphenicol**O**xazolidinones**L**incosamides (clindamycin)**T**etracyclines

## F. Sources obtained from (Source of Origin)

<b>Bacteria</b>	<b>Fungi</b>	<b>Actinomycetes (Soil Microbes)</b>
Polymyxin B	Penicillin	Aminoglycosides
Colistin	Cephalosporins	Chloramphenicol
Bacitracin	Griseofulvin	Macrolides
Tyothricin		Polyenes
Aztreonam		Tetracyclines

## Problems associated with the use of AMAs

### 1. Toxicity

**Local** - Gastric irritation, pain & abscess formation at the site of i.m. injection, thrombophlebitis of the injected vein e.g. **Erythromycin, tetracycline, chloramphenicol and cephalosporins cause irritation**

**Systemic** –

**a. High therapeutic index drugs** (*Penicillins, cephalosporins and erythromycin*) – No apparent damage to host cells

**b. Low therapeutic index drugs**

- **Aminoglycosides:** 8th cranial nerve & kidney toxicity.
- **Tetracyclines:** liver & kidney damage, antianabolic effect.
- **Chloramphenicol :** bone marrow depression

**c. Very Low therapeutic index drugs**

- **Polymyxin B:** neurological and renal toxicity.
- **Vancomycin:** hearing loss, kidney damage, red man syndrome
- **Amphotericin B:** kidney, bone marrow & neurotoxicity.

### 2. Hypersensitivity reactions

All AMAs show hypersensitivity reactions from rashes to anaphylactic shock. **The more commonly involved AMAs in hypersensitivity reactions are—penicillins, cephalosporins, sulfonamides, fluoroquinolones.**

### 3. Drug resistance

- It refers to **unresponsiveness of a microorganism to an AMA**, and is **akin to the phenomenon of tolerance seen in higher organisms**
- **Relative or complete lack of effect of antimicrobial against a previously susceptible microbe.**
  - **Natural Resistance**
  - **Acquired Resistance**

#### a. Natural Resistance

- They **lack the metabolic process or the target site** which is affected by the particular drug.
- **Not a major clinical problem**

**E.g.** Gram-negative bacilli are normally unaffected by penicillin G;

Aerobic organisms are not affected by metronidazole;

Anaerobic bacteria are not inhibited by aminoglycoside antibiotics, or

*M. tuberculosis is insensitive to tetracyclines.*

#### b. Acquired Resistance

- It is the development of resistance by an organism (**which was sensitive before**) **due to the use of an AMA over a period of time.**
- **Major clinical Problem**
- Resistance may be **developed by mutation or gene transfer**
- **Mutation –**
  - It is a stable and heritable genetic change that occurs spontaneously and randomly among microorganisms.
  - **Some cells of sensitive population** of a microbe **converted into few mutant cells** which require higher concentration of the AMA for inhibition.
  - These **mutant cells of microbes preserved** and get a chance to **proliferate when the sensitive cells are eliminated by the AMA.**
  - Then sensitive microbes become resistant toward previous used AMA, e.g. when a single antitubercular drug is used.
  - This is called *vertical transfer of resistance; which is relatively slow and usually of lower grade.*

- **Gene transfer (Also known as infectious resistance)**
  - The resistance causing gene is passed from one organism to the other; is called **horizontal transfer of resistance**
  - Rapid spread of resistance can occur by this mechanism and high level resistance to several antibiotics (multidrug resistance) can be acquired concurrently.
  - Mechanisms involved are: **Conjugation, Transduction, Transformation**
- **Mechanisms of Resistance Development against Microbes**
  - **Resistant organisms can broadly be of the following three types:**
    - (a) **Drug tolerant** - Loss of affinity of the target biomolecule of the microorganism for a particular AMA,
      - e.g. **Rifampin Resistance** – due to development of **RNA polymerase with altered binding site** by resistant *Staph. aureus* and *E. coli*
      - **Penicillin Resistance** – due to **altered penicillin binding proteins** in certain **penicillin-resistant pneumococcal strains**
      - **Trimethoprim Resistance**- due to plasmid mediated synthesis of **dihydrofolate reductase enzyme with altered binding site**
      - **Fluoroquinolone and macrolide resistance** – due to **mutational modification of target site**
  - ❖ **All above mechanisms will lead to decreased binding of respective antibiotics to the target sites of enzymes.**
    - ✚ **Another mechanism is acquisition of an alternative metabolic pathway**, e.g. certain sulfonamide resistant bacteria switch over to utilizing preformed folic acid in place of synthesizing it from PABA taken up from the medium.
  - (b) **Drug destroying** - The resistant microbe **elaborates an enzyme which inactivates the drug**, e.g.
    - (i) **Inactivation of Penicillins by beta lactamases enzyme-**  $\beta$ -lactamases are produced by staphylococci, Haemophilus, gonococci, etc. which **inactivate penicillin G**. The  $\beta$ -lactamases may be **present in low quantity** but strategically **located periplasmically** (as in gram-negative bacteria) so that the drug is inactivated soon after entry, or

may be elaborated in **large quantities** (by **grampositive bacteria**) to **diffuse into the medium and destroy the drug before entry**.

**(ii) Inactivation of Chloramphenicol by acetyl transferase** is acquired by resistant *E. coli*, *H. influenzae* and *S. typhi*.

**(iii) Inactivation of aminoglycosides by enzymes** (produced by resistant coliforms bacteria) **which adenylate/acetylate/phosphorylate** specific aminoglycoside antibiotics

**(c) Drug impermeable (Decreased accumulation)**

- Many **hydrophilic antibiotics gain access into the bacterial cell** through **specific channels formed by proteins called ‘porins’,** or need **specific transport mechanisms**.
- **Decreased uptake or increased efflux of an antibiotic can confer resistance,** because the drug is unable to attain access to the site of its action in sufficient concentrations to injure or kill the organism

E.g. **Some aminoglycosides and tetracyclines** in the **resistant gramnegative bacterial Penicillin-resistant gonococci** are **less permeable to penicillin G;**

**Chloroquine-resistant *P. falciparum*** accumulates less chloroquine.

**Tetracycline, Erythromycin and Fluoroquinolones** acquisition of plasmid directed inducible energy dependent efflux proteins in the cell membrane of **bacteria (known as Active efflux-based resistance)**

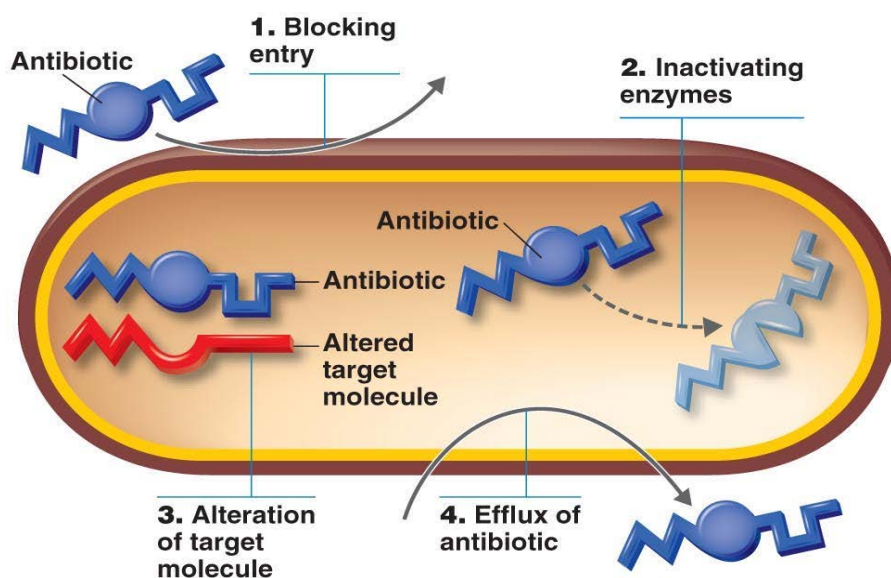


Figure : Resistance Development Mechanisms in Microbes

### Cross resistance

- **Acquisition of resistance to one AMA conferring resistance to another AMA, to which the organism has not been exposed, is called cross resistance.**
- **This is more commonly seen between chemically or mechanistically related drugs, e.g.** resistance to one sulfonamide means resistance to all others, and resistance to one tetracycline means insensitivity to all others.
- Sometimes **unrelated drugs show partial cross resistance**, e.g. between **tetracyclines and chloramphenicol**, between **erythromycin and lincomycin**.
- **Cross resistance may be**
- **two-way, e.g. between erythromycin and clindamycin and vice versa,**  
**or**
- **one-way**, e.g. development of neomycin resistance by enterobacteriaceae makes them insensitive to streptomycin but many streptomycin-resistant organisms remain susceptible to neomycin.

### Factors Promote Antimicrobial Resistance

1. Incompleteness of the course of antibiotic treatment.
2. Forgetfulness to take the doses regularly.
3. Exposure to microbes carrying resistance genes.
4. Use of antibiotics on non-pathogenic microbes lead to conversion of non-pathogenic into pathogenic later on.
5. Use of antibiotics in foods.
6. Antibiotics for viral infections.
7. Spread of resistant microbes in hospitals due to lack of hygiene and used extensively.

### How to prevent drug resistance development in microbes?

1. Avoidance of indiscriminate and inadequate or unduly prolonged use of AMAs
2. Prefer rapidly acting and selective (narrow spectrum) AMAs whenever possible; broad-spectrum drugs should be used only when a specific one cannot be determined or is not suitable.
3. Use combination of AMAs whenever prolonged therapy is undertaken, e.g. tuberculosis, SABC, HIV-AIDS.

4. Infection by organisms notorious for developing resistance, e.g. *Staph. aureus*, *E. coli*, *M. tuberculosis*, *Proteus*, etc. must be treated intensively.

#### 4. Superinfection (Suprainfection)

- It is the **appearance of new or secondary infections** that are **different from original infection** as a result of antimicrobial therapy.
- **Use of most AMAs** causes some **alteration in the normal microbial flora of the body**.
- It can alteration of normal microbial flora of the **upper respiratory, intestinal and genitourinary tract** permitting the over growth especially fungi or resistance bacteria
- These resist to agent being used and **these infections are difficult to treat**.
- **The normal flora contributes to host defence by elaborating substances called bacteriocins which inhibit pathogenic organisms.**
- More complete the suppression of body flora, greater are the chances of developing superinfection.
- It is commonly associated with the use of broad/extended-spectrum antibiotics, such as tetracyclines, chloramphenicol, ampicillin, newer cephalosporins; especially when combinations of these are employed.
- E.g. **Tetracyclines are more liable than chloramphenicol** and **ampicillin is more liable than amoxicillin** to cause **superinfection diarrhoeas** because of incomplete absorption—higher amounts reach the lower bowel and cause **greater suppression of colonic bacteria**.
- **Superinfections are more common when host defence is compromised.**

#### Conditions predisposing to superinfections

- 1) Corticosteroid therapy
- 2) Leukaemias and other malignancies, especially when treated with anticancer drugs (these drugs are also immunosuppressants and decrease WBC count)
- 3) Acquired immunodeficiency syndrome (AIDS)
- 4) Agranulocytosis
- 5) Diabetes, disseminated lupus erythematosus

### How to minimize the chances of Superinfections?

- (i) Use specific (narrow-spectrum) AMA whenever possible.
- (ii) Do not use antimicrobials to treat trivial, self-limiting or untreatable (viral) infections.
- (iii) Do not unnecessarily prolong antimicrobial therapy.

### 5. Nutritional deficiencies

- ✓ Some of the **B complex group of vitamins and vit K synthesized by the intestinal flora** is utilized by man.
- ✓ Prolonged use of antimicrobials which alter this flora may result in vitamin deficiencies.
- ✓ **E.g. Neomycin causes morphological abnormalities in the intestinal mucosa—steatorrhoea and malabsorption syndrome can occur.**

### 6. Masking of an infection

- ✚ It is the suppression of another infection for less time by AMA while using for primary infection and later on this masked or suppressed infection causes severe damage to the host.
- ✚ Examples are:
  - **Syphilis masked by the use of a single dose of penicillin which is sufficient to cure gonorrhoea.**
  - **Tuberculosis masked by a short course of streptomycin given for trivial respiratory infection.**

### Choice of an Antimicrobial Agent

After establishing the use of systemic AMA [if infection is not treatable locally (by antiseptics, drainage of pus etc.) or by itself.

*The choice of antimicrobial use depends on-*

- A. The particulars of the patient,**
- B. The infecting organism and**
- C. The drug (AMAs)**

## A. Patient factors

### 1. Age

Age affects the pharmacokinetic parameters of many AMAs and produces age-related effects.

#### Examples:

- ✚ **Conjugation and excretion** of chloramphenicol is **inefficient in the newborn**: larger doses produce *gray baby syndrome*.
- ✚ **Sulfonamides displace bilirubin from protein binding sites**—can cause kernicterus in the neonate because their blood-brain barrier is more permeable.
- ✚ The  $t_{1/2}$  of aminoglycosides is prolonged in the elderly – cause VIII cranial nerve toxicity (Ototoxicity).
- ✚ **Tetracyclines deposit in the developing teeth and bone**—discolour and weaken them— are contraindicated below the age of 6 years.

### 2. Renal and hepatic function

The dose of low safety margin AMAs should modify in case of renal and liver improper functioning or insufficiency (see boxes below).

Antimicrobials needing dose reduction/avoidance in renal failure	Antimicrobials in liver disease
<i>Reduce dose even in mild failure</i>	<i>Drugs to be avoided</i>
Aminoglycosides      Amphotericin B	Erythromycin estolate      Tetracyclines
Cephalosporins      Ethambutol	Pyrazinamide      Nalidixic acid
Vancomycin      Flucytosine	Talampicillin      Pefloxacin
<i>Reduce dose only in moderate-severe failure</i>	<i>Dose reduction needed</i>
Metronidazole      Carbenicillin	Chloramphenicol      Isoniazid
Cotrimoxazole      Fluoroquinolones	Metronidazole      Rifampin
Aztreonam      Clarithromycin	Clindamycin
Meropenem      Imipenem	
<i>Drugs to be avoided</i>	
Nalidixic acid      Talampicillin	
Nitrofurantoin      Tetracyclines (except doxycycline)	

### 3. Local factors

The conditions prevailing at the site of infection greatly affect the action of AMAs.

- (a) **Presence of pus and secretions - decrease the efficacy of sulfonamides and aminoglycosides.**

*Drainage of the abscess reduces the population of the causative bacteria, suppresses anaerobes by exposure to oxygen, and improves diffusion of the antibiotic into the abscess.*

(b) Presence of necrotic material or foreign body including catheters, implants and prosthesis makes eradication of infection practically impossible.

(c) Haematomas **promote bacterial growth**; tetracyclines, penicillins and cephalosporins get bound to the degraded haemoglobin in the haematoma.

(d) Lowering of pH at the site of infection **reduces activity of macrolide and aminoglycoside antibiotics.**

(e) Anaerobic environment in the centre of an abscess **impairs bacterial transport processes** – decreased accumulation of aminoglycosides in the bacterial cell – bacteria become less susceptible.

(f) Penetration barriers at certain sites may hamper the access of the AMA to the site, such as in subacute bacterial endocarditis (SABE), endophthalmitis, prostatitis.

✓ However, **trimethoprim and fluoroquinolones attain high concentration in prostate due to ion trapping.**

#### 4. *Drug allergy*

If an AMA has produced allergic reaction in previous exposure—it has to be avoided in that patient.

Examples: **drug of choice for syphilis in a patient allergic to penicillin is tetracycline.  *$\beta$ -lactams, sulfonamides, fluoroquinolones and nitrofurantoin frequently cause allergy.***

#### 5. *Impaired host defence*

- ✓ Integrity of host defence plays a crucial role in overcoming an infection.
- ✓ Neutropenic patients are more prone to have pyogenic infections.
- ✓ In an individual with normal host defence, a bacteriostatic AMA may achieve cure; while persons with impaired host defence mechanism require intensive therapy with bactericidal AMA.

## 6. Pregnancy

All AMAs should be avoided in the pregnant woman because of risk to the foetus.

**Safe AMAs in pregnancy are:** Penicillins, many cephalosporins and erythromycin

**Unsafe AMAs in pregnancy are:** Adverse effects due to use during pregnancy

- ✓ **Tetracyclines** – Acute yellow atrophy of liver, pancreatitis and kidney damage. teeth and bone deformities in the mother and offspring.
- ✓ **Aminoglycosides** – foetal ear damage (Ototoxicity).
- ✓ **Fluoroquinolones, cotrimoxazole, chloramphenicol, sulfonamides and nitrofurantoin** – Risk to foetus
- ✓ **Metronidazole** – Not teratogenic but mutagenic

## 7. Genetic factors

**Primaquine, nitrofurantoin, sulfonamides, chloramphenicol and fluoroquinolones** carry the risk of producing haemolysis in **G-6-PD deficient patient**.

## B. Organism-related considerations (Infecting organisms)

Each AMA has a specific effect on a limited number of microbes. Successful chemotherapy must be rational and demands a diagnosis. However, most of the time, definitive bacteriological diagnosis is not available before initiating treatment. Bacteriological testing takes time, is expensive and appropriate samples of infected material for bacteriology may not be obtainable.

**Empirical therapy has to be instituted.** A clinical diagnosis should first be made, at least tentatively, and the likely pathogen guessed.

**The following line of action may be taken:**

1. *Clinical diagnosis itself directs choice of the AMA*
2. *A good guess can be made*
3. *Choice to be based on bacteriological examination*

**Minimum inhibitory concentration (MIC)**, i.e the lowest concentration of an antibiotic which prevents visible growth of a bacterium after 24 hours incubation in microwell culture plates using serial dilutions of the antibiotic is more informative.

**Minimum bactericidal concentration (MBC)** of the antibiotic is determined by subculturing from tubes with no visible growth. If the organism is killed, no growth will occur; but if it was only inhibited in the parent culture—it will grow on subculturing in antibiotic-free medium. **MBC is the concentration of the antibiotic which kills 99.9% of the bacteria.**

**Postantibiotic effect (PAE)** After a brief exposure if the organism is placed in antibiotic-free medium, it starts multiplying again, but after a lag period which depends on the antibiotic as well as the organism. **This lag period in growth resumption is known as ‘postantibiotic effect’ and is the time required for reattainment of logarithmic growth.** It is generally calculated from the time required to attain 10 fold increase in bacterial count in the culture for antibiotic exposed and unexposed tubes. A long and dose-dependent PAE has been noted with fluoroquinolones, aminoglycosides and rifampin.

### C. Drug factors

When any one of a number of AMAs could be used to treat an infection, choice among them is based upon specific properties of these AMAs:

#### 1. Spectrum of activity:

- ✓ For definitive therapy, a **narrow-spectrum drug** which selectively affects the concerned organism is preferred, because it is **generally more effective than a broad spectrum AMA**, and is **less likely to disturb the normal microbial flora**.
- ✓ However, for empirical therapy, often a **broad-spectrum drug has to be used to cover all likely pathogens**.

#### 2. Type of activity:

- ✓ Many infections in patients with normal host defence respond equally well to bacteriostatic and bactericidal AMAs.
- ✓ Several **acute infections resolve faster with a cidal than a static drug**, because the **cidal drug directly reduces the number of bacteria at the site of infection**, while the **static drug only prevents increase in their number**.
- ✓ Many bactericidal drugs exert prolonged postantibiotic effect so that maintenance of drug level continuously above the MIC is not essential.

- ✓ With bacteriostatic AMAs the bacteria start multiplying quickly when drug level falls below the MIC, resulting in relapse of infection.
- ✓ A bactericidal antibiotic is clearly superior to bacteriostatic one in treating patients with impaired host defence, life-threatening infections, infections at less accessible sites (SABE) or when carrier state is possible (e.g. typhoid).

**3. Sensitivity of the organism:** Assessed on the basis of MIC values (if available) and consideration of postantibiotic effect.

**4. Relative toxicity:**

- ✓ Obviously, a **less toxic antibiotic is preferred**, e.g. a  **$\beta$ -lactam over an aminoglycoside** or **erythromycin over clindamycin**.

**5. Pharmacokinetic profile:**

- ✓ **For optimum action the antibiotic has to be present at the site of infection in sufficient concentration for an adequate length of time.**
- ✓ This depends on their pharmacokinetic characteristics.
- ✓ Most antibiotics are **given at 2 to 4 half-life intervals**-thus attaining therapeutic concentrations only intermittently.
- ✓ **Aminoglycosides, fluoroquinolones and metronidazole produce ‘concentration-dependent inhibition’, i.e. inhibitory effect depends on the ratio of peak concentration to the MIC** for many organisms. E.g. The same daily dose of **gentamicin produces better action when given as a single dose than if it is divided into 2–3 portions.**
- ✓  **$\beta$ -lactams, glycopeptides and macrolides produce ‘time dependent inhibition’, i.e. antimicrobial action depends on the length of time the concentration remains above the MIC;** division of daily dose improves the effect.
- ✓ Penetration to the site of infection also depends on the pharmacokinetic properties of the drug.
- ✓ **A drug which penetrates better and attains higher concentration at the site of infection is likely to be more effective.**

- The **fluoroquinolones have excellent tissue penetration** - attain high concentrations in soft tissues, lungs, prostate, joints, etc.
- **Ciprofloxacin and rifampin** have very good intracellular penetration.
- **Cefuroxime, ceftriaxone, chloramphenicol, ciprofloxacin attain high CSF concentration.**
- On the other hand, **penicillins and aminoglycosides penetrate poorly into CSF unless meninges are inflamed.**
- **Ampicillin, cephalosporins and erythromycin attain high biliary concentration.**

#### 6. Route of administration:

- ✓ **Aminoglycosides, penicillin G, carbenicillin, many cephalosporins, vancomycin, etc. - given by injection only.**
- ✓ **Less severe infections - an oral antibiotic is preferable.**
- ✓ **Serious infections** (e.g. meningitis, spreading cellulitis, septicaemias) - **parenteral antibiotic would be more reliable.**

#### 7. Evidence of clinical efficacy:

- ✓ Relative value of different AMAs in treating an infection is decided on the basis of comparative clinical trials.
- ✓ Reliable clinical trial data, if available, is the final guide for choice of the antibiotic.

8. **Cost:** Less expensive drugs are to be preferred.

### Combined use of antimicrobials

It is the use of more than one AMA con-currently to achieve specific aim. The objectives of using antimicrobial combinations are:

#### 1. To achieve synergism

- ✚ Every AMA has a specific effect on selected microorganisms.
- ✚ Depending on the drug pair as well as the organism involved, **either synergism (supra-additive effect), additive action, indifference or antagonism** may be observed when two AMAs belonging to different classes are used together.

✚ **Synergism** – It can be understood by **decrease in the MIC of one AMA in the presence of another, or the MICs of both may be lowered.**

- **If the MIC of each AMA is reduced to 25% or less - pair is considered synergistic**
- **MIC reduced to 25–50% - Each AMA is considered additive**
- **MIC more than 50% - Each AMA indicates antagonism to each other.**

✚ **Advantages of synergism**

- Sensitization of the organisms to the action of the other member of the pair.
- More rapid lethal action of the combination than either of the individual members resulting in faster cure of the infection.
- Synergistic prolongation of postantibiotic effect e.g. combinations of  $\beta$ -lactams with an aminoglycoside, and by addition of rifampin to a variety of antibiotics.

❖ **General guidelines of using two or more AMAs are:**

**(a) Two bacteriostatic agents** are **often additive**, i.e. combination of tetracyclines, chloramphenicol, erythromycin, etc. Examples:

- ✓ Combination of tetracyclines, chloramphenicol, erythromycin, etc.
- ✓ Sulfonamide + trimethoprim = Supraadditive (because of sequential block in folate metabolism of certain bacteria)
- ✓ **The combination often exerts cidal action, while the individual components are only static.**
- ✓ **Combination of a  $\beta$ -lactamase inhibitor clavulanic acid or sulbactam with amoxicillin or ampicillin for  $\beta$ -lactamase producing *H. influenzae*, *N. gonorrhoeae* and other organisms.**

**(b) Two bactericidal drugs** are frequently **additive** and **sometime synergistic** if the organism is sensitive to both, Examples:

- ✓ Penicillin/ampicillin + streptomycin/gentamicin or vancomycin + gentamicin for enterococcal SABC - **Penicillins by acting on the cell wall may enhance the penetration of the aminoglycoside into the bacterium.**
- ✓ Carbenicillin/ticarcillin + gentamicin for *Pseudomonas* infection, especially in neutropenic patients.
- ✓ Ceftazidime + ciprofloxacin for *Pseudomonas* infected orthopedic prosthesis.

✓ Rifampin + isoniazid in tuberculosis.

**Advantages: Combination produces faster cure and reduces the chances of relapse by more complete eradication of the pathogen.**

(c) Combination of a **bactericidal** with a **bacteriostatic** drug may be **synergistic** or **antagonistic** depending on the organism.

(i) **If the organism is highly sensitive to the cidal drug**—response to the combination is equal to the static drug given alone (apparent antagonism), because cidal drugs act primarily on rapidly multiplying bacteria, while the static drug retards multiplication. e.g. **Penicillin + tetracycline/chloramphenicol on pneumococci which are highly sensitive to penicillin.**

Pneumococcal meningitis treated with penicillin + tetracycline had higher mortality than those treated with penicillin alone.

Penicillin + erythromycin for group A *Streptococci* and nalidixic acid + nitrofurantoin for *E. coli* have also shown antagonism.

(ii) **If the organism has low sensitivity to the cidal drug**—synergism may be seen, e.g.: Penicillin + sulfonamide for actinomycosis

Streptomycin + tetracycline for brucellosis

Streptomycin + chloramphenicol for *K. pneumonia* infection

Rifampin + dapsone in leprosy.

## 2. To reduce severity or incidence of adverse effects

This is possible only if the combination is synergistic so that the doses can be reduced.

- **Streptomycin + penicillin G for SABC due to *Strep. faecalis*.**
- **Amphotericin B + rifampin or minocycline:** the latter drugs are not themselves antifungal, but enhance the action of amphotericin B.
- **Amphotericin B + flucytosine:** a **shorter course is needed**, especially for cryptococcal meningitis, than when amphotericin is used alone.

### 3. To prevent emergence of resistance

This principle of using two or more AMAs together is valid primarily for chronic infections needing prolonged therapy; has been widely employed in tuberculosis, leprosy, HIV and now adopted for *H. pylori*, malaria as well.

### 4. To broaden the spectrum of antimicrobial action

This is needed in:

(a) **Treatment of mixed infection** Bronchiectasis, peritonitis, certain urinary tract infections, brain abscesses, diabetic foot infection, bedsores, gynaecological infections are mostly mixed infections. Often, aerobic and anaerobic organisms sensitive to different drugs are involved. e.g.

**Clindamycin or metronidazole** are generally **included to cover anaerobes**.

(b) **Initial treatment of severe infections** For empirical therapy, since bacterial diagnosis is not known; drugs covering gram-positive and gram-negative (in certain situations anaerobes as well), e.g. **penicillin + streptomycin; cephalosporin or erythromycin + an aminoglycoside ± metronidazole or clindamycin**, may be given together.

(c) **Topically** Generally, AMAs which are not used systemically, are poorly absorbed from the local site and cover a **broad range of gram positive and gram-negative bacteria are combined for topical application**, e.g. bacitracin, neomycin, polymyxin B.

### Disadvantages of antimicrobial combinations

1. They foster a casual rather than rational outlook in the diagnosis of infections and choice of AMA.
2. Increased incidence and variety of adverse effects. **Toxicity of one agent may be enhanced by another, e.g. vancomycin + tobramycin and gentamicin + cephalothin produce exaggerated kidney failure.**
3. Increased chances of superinfections.
4. If inadequate doses of nonsynergistic drugs are used—emergence of resistance may be promoted.
5. Higher cost of therapy.

## Prophylactic use of antimicrobials

Prophylaxis is defined as the use of AMAs for **preventing the occurrence an infection or suppressing infection before clinical manifestation**. The latter is also called '**preemptive therapy**', which capitalizes on the small population of pathogen in the body before the disease is manifest. Few examples are:

- **Rheumatic fever: A long acting penicillin G** is the **drug of choice for preventing infection by group A streptococci which cause recurrences**.
- **Tuberculosis:** Children, HIV positive and other susceptible contacts of open cases **Isoniazid alone or with rifampin** is recommended.
- **Mycobacterium avium complex (MAC):** HIV/AIDS patients with low CD4 count may be protected against MAC infection by azithromycin/ clarithromycin.
- **HIV infection:** Health care workers exposed to blood by needle stick injury are to be protected by zidovudine + lamivudine ± indinavir.
- Offspring of HIV positive woman can be protected by zidovudine given to pregnant mother and then to the newborn for 6 weeks.
- **Meningococcal meningitis:** rifampin/ sulfadiazine/ceftriaxone may be used.
- **Gonorrhoea/syphilis:** ampicillin/ceftriaxone.
- **Recurrent genital herpes simplex:** Acyclovir prophylaxis
- **Malaria:** Travellers to endemic areas with high transmission rate many be covered by mefloquine or doxycycline.
- **Influenza A2 :** amantadine
- **Cholera:** tetracycline
- **Whooping cough:** non-immunized child contact during the incubation period: **erythromycin can abort clinical disease**.
- **Plague:** Doxycycline prophylaxis
- **Pneumocystis jiroveci pneumonia:** Transplant recipients on immunosuppressants/ leukaemia or AIDS patients may be protected by cotrimoxazole.
- **Catheterization or instrumentation of urinary tract:** prophylaxis with cotrimoxazole or norfloxacin decreases the risk of urinary tract infection (UTI). Patients with cardiac valvular lesions may be protected with ampicillin, gentamicin or vancomycin during catheterization.

- **Chronic obstructive lung disease, chronic bronchitis:** ampicillin/ doxycycline/ ciprofloxacin has been used to prevent acute exacerbations.
- **Immunocompromized patients (receiving corticosteroids or antineoplastic chemotherapy or immunosuppressants after organ transplantation, neutropenic patients):** penicillin/cephalosporin ± an aminoglycoside or fluoroquinolone are often used to prevent respiratory tract infections and septicaemia, but incidence of superinfections is high.

### Prophylaxis of surgical site infection

- ✓ **Surgical site infection (SSI) includes superficial incisional infections (e.g. stitch abscess), deep incisional infection (of soft tissue) and organ/ space infection.**
- ✓ The **purpose of surgical prophylaxis** is to **reduce the incidence of SSI with minimal alteration of normal microbial flora of the host and minimal adverse effects.**
- ✓ The selection of drug, dose, timing and duration of prophylactic medication is crucial.
- ✓ It is important that the antibiotic is not started prematurely and is not continued beyond the time when bacteria have access to the surgical wound.

<b>Commonly used antimicrobials drugs for surgical prophylaxis</b>	
<i>Oral (single dose given 1 hour before procedure)</i>	
1. Amoxicillin 2 g (50 mg/kg)	
2. Cephalexin 2 g (50 mg/kg)	
3. Cefadroxil 2 g (50 mg/kg)	
4. Clindamycin 600 mg (20 mg/kg)	} For patients allergic to penicillin
5. Azithromycin 500 mg (15 mg/kg)	
6. Clarithromycin 500 mg (15 mg/kg)	
<i>Parenteral (single injection just before procedure)</i>	
1. Ampicillin 2 g (50 mg/kg) i.m./i.v.	
2. Cefazolin 1 g (25 mg/kg) i.v.	
3. Vancomycin 1 g (20 mg/kg) i.v. (in MRSA prevalent areas and/or penicillin allergic patients).	
4. Clindamycin 600 mg (20 mg/kg) i.v. (for penicillin allergic patients).	
5. Cefuroxime 1.5 g (30 mg/kg) i.v.	} For gut and biliary surgery
+ Metronidazole 0.5 g (10 mg/kg) i.v.	
6. Gentamicin 160 mg (3 mg/kg) i.v.	
+ Metronidazole 0.5 g (10 mg/kg) i.v.	

## **Failure of antimicrobial therapy**

The success of antimicrobial therapy can be measured either clinically in terms of improvement in symptoms/signs or microbiologically as eradication of the infecting organism. Antimicrobials may fail to cure an infection/ fever, or there may be relapses.

### **Causes for failure of Antimicrobial therapy**

1. Improper selection of drug, dose, route or duration of treatment.
2. Treatment begun too late.
3. Failure to take necessary adjuvant measures, e.g. drainage of abscesses, empyema, etc.; removal of renal stones, other foreign bodies or infected gall bladder, adjustment of proper urinary pH in case of UTI; cavity closure; control of diabetes, etc.
4. Poor host defence—as in leukaemias, neutropenia and other causes, especially if a bacteriostatic AMA is used.
5. Infecting organism present behind barriers, such as vegetation on heart valves (SABE), inside the eyeball, blood brain-barrier.
6. Trying to treat untreatable (viral) infections or other causes of fever (malignancy, collagen diseases).
7. Presence of dormant or altered organisms (the persisters) which later give rise to a relapse.