Resistance to antimicrobial drugs

- Antimicrobial resistance can be developed at any step from its site of absorption till the elimination of drugs. There are following mechanisms by which microorganism exhibits resistance to anti-microbials.
- 1. **Production of enzymes:**
- Microorganism produce enzymes that destroy antibiotics. e.g Staphylococci produce ß-lactamase enzyme that destroy ß-lactam antibiotics (Penicillin, cephalosporins, etc.)
- Gram (-) bacteria resistant to Chloramphenicol produce chloramphenicol acetyl transferase enzyme that destroy chloramphenicol.

Mechanism of resistance…….

- **2. Change in permeability:**
- The outer membrane of gram (-) bacteria (e.g Streptococci) is a permeable barrier that prevent entry of polar molecules. Such polar drugs (Aminoglycosides) enter through porin channels present in membrane. Mutation or loss of porins in bacteria develop resistance against aminoglycosides.
- **3. Resistance due to drug efflux:**
- Microorganism can overexpress efflux pumps that expel out antibiotics. E.g Plasmodium falciparum show resistance against antimalarial through efflux mechanism. Mycobacterium tuberculosis against anti-TB drugs.
- The efflux may be due to followings:
- The multidrug and toxic compound extruder, small multidrug resistance system, major facilitator superfamily transporters, ATP binding cassette transporters etc.

Mechanisms of resistance…….

- **4. Altered target site/reduced affinity:**
- Alteration at single or multiple points reduce or loss of drug affinity. Such alterations may be due to mutation of the natural target. E.g microbial resistance against fluoroquinols.
- Similarly Methicillin resistant Staphylococci show resistant against penicillin G due to low affinity penicillin binding protein.
- **5. Alteration in enzymes or metabolic pathways:**
- E.g dihydropteroate synthase enzyme has higher affinity with PABA as compared to Sulphonamides. Similarly microorganism alter metabolic pathways and show resistance against sulphonamides.

Selection of Antimicrobials to treat infectious diseases

Dr. Hafiz Muhammad Irfan, Assistant Professor

College of Pharmacy, University of Sargodha

1. Sensitivity/SusceptibilityTesting

- Microorganisms are categorized into: Bacteria, Viruses, Fungi and parasites.
- Antimicrobial drugs are categorized depending upon their susceptibility against particular microorganism into anti-bacterial, anti-viral, anti-fungal and anti-parasitic.
- Identification and isolation of microorganism is first step in selection of anti-microbial drugs in cultures of blood and certain other body fluids/tissues.
- Gram staining can be of much help in identification and narrowing the list of potential pathogens and give a clue for more rational start of therapy.

Susceptibility/sensitivity testing……

- Across the world, healthy individuals are get infected by many different strains of the same species of pathogens. Evolutionary processes cause each strain (isolate) to be slightly different from the next. So each will have a unique susceptibility to anti-microbial drugs.
- Within the patients, the microorganism may also go for evolution between the time of infection. For example in HIV infection, each day multiple replication may result in variation in last replicate.
- Changes in isolates, changes the its susceptibility to a particular antimicrobial drugs. The sigmoid curve may shift towards right means an increase in IC50.
- Indicates that much higher concentration is needed to show specific effect.

Susceptibility/sensitivity testing……

- To check susceptibility, two methods are employed
- 1. Disk diffusion method
- 2. Broth dilution method

2. Antimicrobial therapy

- Generally two antimicrobial therapies are used:
- 1. Empirical therapy
- 2. Definitive therapy
- Empirical therapy means the treatment of infectious disease with antibiotic in critically ill patients before the identification and sensitivity testing of the causing microorganism.
- Definitive therapy means the treatment of infection with highly selective and most suitable antimicrobials after identification and susceptibility.
- Ideally the start of antibiotic therapy must be done after proper identification and susceptibility testing

3. Pharmacokinetic parameters

- The success of every therapy depends upon that how much concentration of drug is available in the systemic circulation. If you get the required amount, you will get the therapeutic response.
- Similarly, until and unless you don’t get the MIC in the plasma, antimicrobial effect will not produced. That’s why absorption, distribution, metabolism and excretion are very important.
- Sometimes the pathogens causes disease in specific organs/ compartments in these organs. Therefore antibiotic should penetrate in that specific site.

Pharmacokinetic parameters…….

- The penetration of drug into compartment depends upon:
- (1) **Physical barriers** e.g layers of epithelial and endothelial cells
- (2) **Presence of multidrug transporters:** Membrane transporters which actively transport drugs from the cellular or tissue compartment back into bloog- P-glycoprotein. The antimicrobial drugs that are substrates for P-glycoprotein are: Telithromycin, Itraconazole, protease inhibitors.
- and **(3) chemical properties of the drug:** Hydrophilicity/ hydrophobicity of drug molecule. Polar antibiotic e.g Penicillin G penetrate poorly
- Once an antibiotic has penetrated to the site of infection, then it is subjected to elimination. For elimination, drugs follow either first order (directly correlated to concentration of drug or zero order which is independent of drug.

4. Route of administration

- Oral route is preferred, but in seriously ill patients, parenteral administration is selected to achieve plasma therapeutic level.

5. Antibiotic concentration at infection site

- Adequate concentration should reach at the infection site. There are certain barriers that come across in penetration of drugs in certain tissues.
- For example (1) Blood Brain Barrier (BBB) reduce penetration of polar drugs in CSF. (2) Plasma protein binding (PPB) the rate of penetration is proportional to concentration of free drug in plasma. Extensively PPB drug may diffuse poorly so such have lesser activity. Quinine 80% bound to plasma protein and chloroquine 50 -65% PPB. (3) Prostate epithelium- prevent entry of many antimicrobial drug and ineffective them in the treatment of prostate infection. Norfloxacin, co-trimoxazole effective in prostate infection.

6. Status of patient

- **Renal dysfunction** may lead to the accumulation of those antibiotics which are excreted through kidney. Aminoglycosides, penicillins, vancomycin primarily excreted through kidney.
- **Hepatic impairment** may lead to accumulation of those which are metabolized through liver. E.g Erythromycin, Chloramphenicol, Metronidazole etc.
- **Age:** Use of chloramphenicol in new born may result in Gray baby syndrome. The use of tetracycline impair development of bone in children. Achlorhydria in elderly patient may alter absorption of orally administered antibiotics.
- **Pregnancy:** Most of antibiotics cross placental barrier and may harm to fetus. E.g Streptomycin cause hearing loss, Tetracycline affect bone growth.

Status of patients……..

- **Lactation:** Antibiotics excreted in milk may cause problem in babies. E.g. Nalidixic acid, Sulphonamides may cause hemolysis in children with Glucose-6-phosphate dehydrogenase deficiency.
- **Drug Allergy:** β-lactam antibiotics and Sulphonamides may initiate hypersensitivity reactions.
- **Host defense mechanism:** In immune-competent patients, bacteriostatic drugs are enough to eradicate microbes while bactericidals are needed in immune-compromized patients or combination chemotherapy.

7. Dose and Dosing schedule

- The optimal dose of an antibiotic is the dose that achieves IC80 to IC90 exposure at the site of infection with suppression of resistance. Similarly antibiotics are prescribed at a certain dosing schedule means one a day, twice or thrice a day to maintain optimal antibiotic concentration at the site of infection. For this half life of antibiotic and incubation period of microorganism are considered. Because improper dose and dosing schedule may result in super infection.

8. Cost of therapy

- For patient compliance the therapy total cost is very crutial as compliance is directly proportional to the socioeconomic status of patient.