The importance of antibiotics

Antibiotics have been called as the single most important therapeutic discovery in the history of medicine. An interesting feature of their historic discovery is that they occur within the lifetime of many populations living today. The most important event in the discovery of antibiotics occurred around 1940 and began the era of antibiotics. Although Alexander Fleming discovered penicillin in 1929, it was only recognised for its potential and potency by Florey and its team in 1940. Antibiotics were once called as “ wonder drugs.” These drugs have been used for decades to treat effectively a wide variety of bacterial infections. If it is left untreated many of these bacterial infections would have been deadly. 1

ANTIBIOTICS:

Antibiotics are substances produced by various species of micro-organisms(bacteria, fungi, and actinomyctes) that suppress the growth of other Micro-organisms and eventually may destroy them. This definition excludes other natural substances which also inhibit micro-organisms but are produced by microbes that are needed in high concentrations(ethanol, lactic acid, hydrogen peroxide).

CLASSES OF ANTIBIOTICS:

Antibiotics are classified in many ways. The classification is based on the organisms range killed by the antibiotic. This method of classification involves in two classes:

Spectrum of activity:

Broad spectrum antibiotics : Tetracycline, Chloramphenicol

Narrow spectrum antibiotics : Pencilline G, streptomycin, Erythromycin

Type of action:

Bacteriostatic : Sulfonamides, Erythromycin,

Tetracyclines, Ethambutol

Bacteriocidal : Pencillins, Cephalosporins,

Aminoglycosides, Vancomycin,

Polypeptides, Nalidixic acid,

Rifampin, Ciprofloxacin, Cotrimoxazole

Some which are primarily static drugs may become cidal at higher concentrations (as attained in the urinary tract), e. g. Sulphonamides, Erythromycin, Nitrofurantoin. On the other hand, some cidal drugs may only be static under certain circumstances, e. g. Cotrimoxazole, Streptomycin.

c) Mechanism of action:

1. Inhibit cell wall synthesis : Pencillins, Cephalosporins,

Cycloserins, Vancomycin, Bacitracin

2. Cause leakage from cell membranes : Polypeptides – Polymixins,

Colistin, Bacitracin,

Polyenes – Amphotericin B, Nystatin, Hamycin

Inhibit protein synthesis : Tetracyclines,

Chloramphenicol, Erythromycin, Clindamycin, Linezolid

Cause misreading of m-RNA code and affect permeability :

Aminoglycosides : Streptomycin, Gentamycin

Inhibit DNA gyrase : Fluroquinolones – Ciprofloxacin

Interfere with DNA function : Rifampin, Metronidazole

Interfere with DNA synthesis : Idoxuridine, Acyclovir, Zidouidine.

Interfere with intermediary metabolism : Sulfonamides, Sulfones, PAS, Trimethoprim, Pyremethamine, Ethambutol.

Chemical structure

Sulfonamides and related drugs : Sulfadiazine and others,

Sulfones- Dapsone, Paraaminosalicylic acid. Diaminopyrimidines: Trimethoprim, Pyrimethemine.

Quinolones : Nalidixic acid, Norfloxacin,

Ciprofloxacin, Ofloxacin,

Gatifloxacin, Lomefloxacin, Perfloxacin, etc

Î² – Lactum antibiotics : Penicillin, Cephalosporins,

Monobactums, Carbapenems.

Tetracyclines : Oxytetracyclines,

Doxycycline, etc

Nitrobenzene derivatives : Chloramphenicol.

Aminoglycosides : Streptomycin, Gentamycin,

Neomycin, Amikacin, etc

Macrolide antibiotics : Erythromycin, Roxithromycin,

Azithromycin, etc

Polypeptide antibiotics : Polymyxin- B, Colistin, Bacitracin,

Tyrothicin.

Glycopeptides : Vancomycin, Teicoplanin.

Oxazolidinone : Linezolid.

Nitrofuran derivative : Nitrofurantoin, Furazolidone.

Nitroimidazoles : Metronidazole, Tinidazole.

Nicotinic acid derivatives : Isoniazid, Pyrazinamide, Ethionamide.

Polyene antibiotics : Nystatin, Amphotericin-B, Hamycin.

Azole derivatives : Miconazole, Clotrimazole,

Ketoconazole, Fluconazole.

Others : Rifampin, Lincomycin,

Clindamycin, Spectinomycin, Sodium fusidate, Cycloserine, Ethambutol,

Thiacetazone, Clofazimine, Griseofulvin.

Type of organism against which primarily active:

Antibacterial : Penicillins, Aminoglycisides, Erythromycin.

Antifungal : Griseofulvin, Amphotericin- B, Ketoconazole.

Antiviral : Idoxuridine, Acyclovir, Amantiadine, Zidovudine

Antiprotozoal : Chloroquine, Pyremethamine, Metronidazole,

Diloxanide.

Antihelmintic : Mebendazole, Pyrantel, Niclosamide, Diethyl

Carbamazepine, etc.

Antibiotics are obtained from:

Fungi : Penicillins, Griseofulvin, Cephalosporins

Bacteria : Polymixin-B, Tyrothricin, Colistin, Azetrenam,

Bacitracin.

Actinomycetes : Aminoglycosides, Macrolides, Tetracycline,

Polyenes, Chloramphenicol.

MECHANISM OF ACTION:

Penicillin

They act by inhibiting the enzymes (Penicillin Binding Proteins) involved in the cross linking of the peptidoglycan layer of the cell wall which protects the bacterium from its environment; incapable of withstanding the osmotic gradient between its interior and its environment the cell swell and ruptures.

Penicillin are thus bactericidal and are effective only against multiplying organisms because resting organism are not making new cell wall.

Cephalosporins

They impair bacterial cell wall synthesis, and hence are bactericidal. They exhibits time dependent bacterial killing.

Aminoglycosides

They act inside the cell by binding to the ribosomes in such a way that correct amino acid sequences are entered into peptide chains. The abnormal properties which results are fatal to the microbe, ie, aminoglycosides are bactericidal and exhibit concentration dependent bacterial killing.

Tetracyclines

Tetracyclines have abroad range of antimicrobial activity and differences between the individual members are in general small. These agents interfere with protein synthesis by binding to bacterial ribosomes and their selective action is due to higher uptake by bacterial than by human cells. They are bacteriostatic. S

Quinolones

They act mainly by inhibiting the bacterial DNA- gyrase, so preventing the supercoiling of DNA, a process that is necessary for compacting chromosomes into the bacterial cell; they are bactericidal and exhibit concentration- dependent bacterial killing. 2

SELECTION OF ANTIMOCROBIAL AGENTS:

Although it is necessary to begin the treatment in critically ill patients before culture and sensitivity tests are completed, culture specimen should always be taken before therapy begins. Culture identifies the causative organism and susceptibility determines which drugs are likely to be effective against the organism. Culture and susceptibility studies are always important with suspected gram negative infections because of high incidence of drug-resistant organisms. The natures of illness, the toxicity of drug, the patient's history of hypersensitivity are other serious reactions and the cost of antibiotics must also be considered before prescribing an antibiotic.

CAUSES OF FAILURE OF ANTIMICROBOAL AGENT:

Failure to use laboratory properly:

Specimens may not have been collected before the start of antibiotic therapy and this is especially serious if there is a life threatening infection present such as infective endocarditis.

Limitations of laboratory methods and laboratory errors:

The laboratory may fail to recognise the causative organism of infection in good quality of specimens, either because of lack of severity of diagnostic methods or because of technical errors.

Clinical condition not susceptible to antimicrobial treatment:

A frequent cause of apparently failed therapy is the hidden collection of substantial quantity of pus which ne4eds to be located and surgically

drained. In some cases an infection may be present but may not respond to antibiotic treatment such as glandular fever.

Wrong choice of antibiotics:

The choice of drugs is influenced by patient factors. Ideally a narrow spectrum antibiotic should be selected for treating specific infections.

Inadequate duration:

Relapses of infection may occur if a full course of antibiotic is not completed.

Misuse of antibiotics:

Antibacterial drugs are often used without valid indications such as for viral illness or are used improperly. Common misuse and errors include choosing an ineffective antibiotic, giving inadequate/excess dose, treating non-bacterial infections such as uncomplicated viral disease, using improper route of administration, continuing in the presence of a serious toxic or allergic reactions, continuing use after bacterial resistance has developed, prematurely stopping the therapy or prophylaxis to the exclusion of surgical intervention.

Development of antimicrobial resistance:

Antimicrobial resistance is currently the greatest challenge to the effective treatment of infections globally. Resistance adversely effects both clinical and financial therapeutic outcomes, with effects ranging from the failure of the individual patient to respond to therapy and the need for expensive alternative drugs to the social costs of higher morbidity and mortality rates, longer duration of hospitalization, and the need for changes in empirical therapy. Multiresistantorganisms are diminishing our ability to treat and

control the spread of the infections. Abuse and misuse of antibiotics have been known to contribute the development of antibiotic resistance. Clinicians frequently commence patients on antibiotic therapy before sending samples to the microbiology laboratory for culture sensitivity analysis. 3

EMERGENCE OF RESISTANCE:

All uses of antimicrobial drugs both appropriate and inappropriate apply a selective pressure on the microbial populations. However, the more antimicrobials are used the more problem. Thus, it is critical to gain maximum benefit from curative effects of these drugs especially in developing countries, when they are not only misused but also underused due to their financial constraints. In practice this means using antimicrobials wisely neither too little nor too much and never inappropriately.

REASONS FOR ANTIBIOTIC RESISTANCE:

Epidemic use of antibiotics:

Epidemic use of antibiotics has contributed to the development of bacterial resistance in the community. Resistance to macrolides, Doxycycline, Trimethoprim and second and third generation cephalosporin’s have increased.

Previous antibiotic use – An important risk factor:

Numerous retrospective prospective studies have shown that previous antibiotic use especially for a prolonged period to be the most significant risk for the carriage and subsequent spread of antibiotic resistant S. pneumoniae. the risk of carriage of antibiotic resistance is 2-9 times greater in persons who have recently used antibiotics. 4

EPIDEMIOLOGY OF ANTIBIOTIC RESISTANCE:

The incidence of antibiotic resistance in strains of different bacterial species depends on three main factors namely:

The occurrence of plasmids, or transposons and certain chromosomal genes, which mediate drug resistance in bacteria.

The patterns of antimicrobial drug use in hospital or in general population.

The greater the quantity of drugs used and the longer the drugs have been in use, the more likely it is that the strains develop resistance to antibiotics. Certain types of usage are strongly associated with development of resistance, such as the topical use of gentamicin, or neomycin leads to the development of resistant strains to these antibiotics.

The degree of cross infection with antimicrobial -resistant strains of bacteria. This is particularly relevant in hospitals. 3

MECHANISM OF ANTIMICROIBIAL RESISTANCE:

Antimicrobial resistance to antibiotics is a matter of great importance if sensitive strains are supplanted by resistant ones, then a valuable drug may become useless. Based on the mechanism, resistance can be classified as:

Naturally acquired resistance.

Acquired drug resistance.

Tolerance (adaptation).

‘ Single step’ chromosomal mutation.

Transmissible drug resistance.

Naturally acquired resistance:

An entire bacterial species may be resistant to an antibiotic before the introduction of the drug. Reasons for innate drug resistance include lack of penetration of drug through the cell wall, lack of a suitable cell wall target site and susceptibility to naturally produced drug destroying enzymes Eg: S. pyogens resistant to gentamicin.

Acquired drug resistance:

The two many groups of antimicrobial drug resistance mechanism are mechanisms involving drug destroying enzymes and intrinsic type of resistance.

Drug destroying enzymes

Penicillinases and cephalosporin are Î²-lactamases which hydrolyse the Î²-lactam ring of various Cepahalosporins and Penicillins. During destroying enzymes are responsible for high level antibiotic resistance in some Gram negative bacilli including resistance to many aminoglycosides.

Eg: some E. coli strains are resistant to kanamycin or streptomycin but susceptible to gentamicin.

Intrinsic type of resistance

Permeability barriers to drugs can be developed by an intrinsic resistance mechanism. This occurs with tetracycline resistance in some S. aureus strains. Development of an altered metabolic pathway can allow bacterial strains to be no longer inhibited by drug. For examples sulphonamides

resistance in E. coli strains, can be due to these strains requiring less extracellular p- amino benzoic acid for folic acid synthesis.

Alteration of a target site in the cell is a frequent mechanism of drug resistance. Examples include alteration of ribosome binding sites for some aminoglycosides, as seen in streptomycin resistant S. aureus.

Methicillin resistant S. aureus strains are due to an altered penicillin binding protein in the cell wall and this is chromosomes rather than plasmid mediated. There is some cross- resistance in these strains between Methicillin and Cloxacilin, Flucloxacilin and Cephalosporin.

Tolerance (adaptation):

There are many examples of laboratory ‘ training’ of organism to become gradually adapted to grow in the presence of increasing concentrations of a drug and such an adaptive process is often not important clinically. However, there are some instance3s of the gradually development of low levels of drug resistance in clinical isolates.

Eg: over the years gonococcal strains are difficult to treat unless penicillin is given in enormous doses.

‘ Single step’ chromosomal mutations:

The rapid development of high level of antimicrobial drug resistance in an infective strain may occur during the course of treatment when the drug is used alone. This particularly applies in staphylococci to streptomycin, rifampicin and erythromycin. For the above drugs, the development of resistance mutants can occur at a relatively high frequency and once

resistant mutants appear, they become selected out in presence of the drug so that after a short time only drug- resistant mutants are isolated from the patient.

Eg: a high degree of resistance can appear due to a single base change in the DNA ofE. coli so that the ribosome is altered and is no longer susceptible to the action of streptomycin.

Transmissible drug resistance:

It is now realizes that most of the clinically important acquired drug resistance in antibiotic – resistance strains ofS. aureus and certain Gram negative bacilli are ‘ R’ factor (plasmid) mediated. Plasmids are extra chromosomal packets of DNA which may code for antibiotic resistance and be transferred from an antibiotic – resistant strain to a sensitive strain, thereby causing the sensitive strain to become antibiotic – resistant.

This gene transfer in bacteria occurs by three mechanisms namely: Conjugation, Transduction and Transformation. 3

CONTROL OF ANTIMICROBIAL RESISTANCE:

The discoveries of antibiotics have revolutionized the treatment options for patients treated with bacterial infections and have helped to cause a greater reduction in mortality and morbidity from bacterial diseases. These potent antibiotics are an absolutely necessary tool in the field of modern medicine and commonly carried out procedures such as transplants, chemotherapy for cancer and even orthopaedic surgery, without which these procedures cannot be performed.

Antibiotics are unfortunately very much liable to misuse. Unnecessarily antibiotics are often prescribed for viral infections, against which they do not produce much effect. In diagnoses that are not performed accurately, more often than not, broad-spectrum antibiotics, i. e. antibiotics that kill a large proportion of various bacteria and not only the bacteria responsible for the disease, are prescribed because the micro-organism responsible for the infection is not known. These instances which cause the misuse of antibiotics promote the emergence and the selection of resistant bacteria.

Considering the mechanisms behind the emergence of antimicrobial resistance proves that strategy to fight it is rather straightforward:

Use less antibiotics, i. e. only when they are needed to treat patients.

Prevent the spread of resistant strains between persons. 5

Some of the methods to control antibiotic resistance are:

Limiting the Spread of Drug Resistant Bacteria

Several measures could be used to prevent the spread of drug resistant bacteria.

First, we could use better treatment strategies; better immunization programmes; improved hygiene and nutrition; and initiatives targeting the poor populations.

Second, it might be useful to establish antibiotic resistance surveillance programmes.

Third, better education of health care professionals is required to prevent the prescription of unnecessary antibiotics.

It is noteworthy that significant investment of time, effort, and money is necessary in order to control antibiotic resistant bacteria. Of course, as long as antibiotics are used, antibiotics resistance is bound to occur. However, we might be able to reduce the drug resistance problem. One strategy is to ensure that antibiotics are used only when necessary. A second strategy is to ensure that they are used for the appropriate amount of time, that is, that the treatment is not stopped before it iscompleted. Patient compliance is a key problem in that respect. A third strategy for limiting drug resistance is to use antibiotics combinations. Unfortunately, while all these strategies seem sound in theory, in reality, the problem persists.

2. Development of New Antibiotics

Another possibility is to develop new antibiotics. However, that is not an easy task. The sad irony is that many pharmaceutical companies have decided to abandon their antibiotic development programmes when new antibiotics are needed most, since 99% of the drug candidates fail, and antibiotics are not as profitable as other, more commonly used, drugs. The traditional approach of screening microbes for antibiotics is not efficient. A second approach, which utilises target-based screening, became popular when genomics tools became available. However, although the idea is appealing, in reality, it is extremely difficult. Many companies have tried this approach, and so far they have all failed. The whole organism-based approach is more feasible but the conditions of screen need careful consideration.

3. Phage Therapy

Phage therapy can also be used to deal with antibiotics resistance. This approach had already been used by the Russians during the Second World War, and has been gaining popularity again in recent years. Phage can be applied on the wounds of a patient to kill the bacteria, and has proven to be quite effective. Of course, it cannot be used for internal infections, and the bacteria might also develop phage resistance.

4. Mobilisation of Host Defence Mechanisms

Yet another approach is to mobilise host defence mechanisms. This can be achieved through the mobilisation of innate immunity such as defensins, or through the development of vaccines, which make antibiotics less necessary. The idea is to boast the immune response capability to control the bacterial infection. Of course, that approach is not always successful.

5. The Use of Normal Bacterial Flora

Finally, one could also potentially use normal bacterial flora to suppress some pathogen. 6

In hospitals effective prevention of cross infection and development of strict antibiotic policies should be in the hands of experts. Each hospital thus needs infectious disease specialists, clinical microbiologists, infection control nurses and sufficient resources to run the program.

Research is also a cornerstone in the fight against bacterial resistance. New diagnostic technologies to enable rapid identification of viral and bacterial infections are also necessary.

Thus continous monitoring of the pattern of bacterial resistance serves as empiric guide for therapy. 7

IMPORTANCE OF CULTURE AND SENSITIVITY IN ANTIBIOTIC THERAPY:

In modern laboratories, bacteria are usually identified by characterization of the genome: identifying the characteristics of the DNA and RNA of a sample species. This type of testing is generally considered more reliable than actually growing bacterial cultures and exposing them to various types of antibiotics to see which drugs kill or inhibit the bacterial growth. But if more than identification is required, and if an antibiotic that usually works against a particular bacterial strain is ineffective, then it may be necessary to actually grow the bacteria and perform an “ old fashioned” culture and sensitivity test. 8

Empirical therapy should be given when bacterial infection is suspected and poses a sufficient health risk to demand immediate treatment.

Eg: tuberculosis, UTI, PUO.

Problems with empirical therapy are:

Prescribing antibiotics to patients who donot have bacterial infection.

Inappropriate antimicrobials may be selected.

It is common to use broad spectrum agents or combinations. 9

The importance of determining the type and sensitivity of causative organism is obvious. The key action by the clinician should be the provision

of specimen for accurate identification of the offending pathogen by means of culture and sensitivity method.

PURPOSE OF CULTURE:

Microbial cultures are used to determine the type of organism, its abundance in the sample being tested, or both. It is one of the primary diagnostic methods of microbiology and used as a tool to determine the cause of infectious disease by letting the agent multiply in a predetermined media. For example, a throat culture is taken by scraping the lining of tissue in the back of the throat and blotting the sample into a media to be able to screen for harmful microorganisms, such as Streptococcus pyogenes, the causative agent of strep throat. Furthermore, the term culture is more generally used informally to refer to “ selectively growing” a specific kind of microorganism in the lab.

Microbial cultures are foundational and basic diagnostic methods used extensively as a research tool in molecular biology. It is often essential to isolate a pure culture of microorganisms.

BACTERIAL CULTURE:

A portion of the specimen is smeared on a microscope slide for Gram stain. Another portion is spread over the surface of different types of culture plates and placed in an incubator at 37° for one or two days. Gram staining checks the colour picked up by the bacteria, their shape and size provide valuable clues to their identity and helps the physician predict what antibiotics might work best before the entire test is completed. Bacteria that stain purple are Gram positive, those that stain red are Gram negative. During incubation

bacteria present in the specimen multiply and will appear on the plates as visible colonies.

The final report usually available in one or three days includes complete identification and an estimate of the quantity of the bacteria and list of antibiotics to which they are sensitive.

PREPARATION:

The specimen for culture should be collected before the antibiotics are begun. Antibiotics in the persons system may prevent microorganism present in the specimen from growing in culture. The best time to collect the specimen is early in the morning, before having anything to eat or drink.

Specimen from healthy person would have no growth on culture. A mixture of micro-organisms however is present as normal flora.

The specific knowledge about bacterial pathogens in patients allows treatment with antibiotics that are usually narrow spectrum, cheaper and specific for the organism. 10

ROLE OF PHARMACIST IN COMBATING RESISTANCE:

Over the last 60 years, bacteria, and in particular those pathogenic for humans have evolved towards antimicrobial drug resistance. The evolution has two key steps: emergence and dissemination of resistance.

It is imperative that all the clinicians understand the principles and standard methods of antibiotic susceptibility tests. They should also insist on

laboratory to follow these recommended procedures to generate antibiotic susceptibility

Test reports that are quality assured. Antimicrobial susceptibility data generated based on consistent, reproducible and comparable data between different laboratories will produce better outcomes and help in developing region wiseantibiograms.

Sharing of expertise, cooperation and collaboration between the clinicians using antibiotic therapy and the clinical microbiologists at the regional levels may be the simplest and most useful public health measure to optimize the use of antibiotics and manage infectious diseases.

Pharmacists have a role to play, it is increasingly apparent that there is a need to develop and expand education programmes to create more clinical specialists with a particular expertise in antibiotic prescribing. Nationwide education, training and accreditation for antibiotic pharmacists should be promoted. Their role would ideally include reviewing antibiotic orders (including drug selection and duration of therapy), design and promotion of clinical practice guidelines, implementation and operation of antibiotic “ switch” programmes and documenting the effectiveness of interventions. As, in many European countries, the concept of an antibiotic pharmacist is a relatively new one, it will be necessary to study the effect of the role of these specialists on improving and reducing antibiotic prescribing to encourage the establishment of such posts. 11