EVALUATION OF ANTIMICROBIAL AGENTS PRESCRIBED BY UNIVERSITI SAINS MALAYSIA PANEL OF DOCTORS: A PHARMACOEPIDEMIOLOGY APPROACH

by

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LIST OF ABREVIATIONS

Ab	Antibiotic
AGE	Acute Gastro Enteritis
CF	Claim Form
DUR	Drug Utilization Review
EDC	Essential Drug Concept
EDL	Essential Drug List
ENT	Eye, Ear, Nose, Throat
USM	Universiti Sains Malaysia
MSTG	Malaysian Standard Treatment Guideline
NO	Number
n	Number of prescription
RM$	Ringgit (Malaysian currency)
SPSS	Statistical Package for Social Sciences
URTI	Upper Respiratory Tract Infection
UTI	Urinary Tract Infection
U	Unwritten
WHO	World Health Organization
W	written

Penilaian Preskripsi Antimikrobial di Kalangan Doktor Panel USM: Pendekatan Farmakoepidemiologi

Abstrak

Kajian penggunaan drug adalah penting untuk menentukan tahap penggunaan drug dalan sesebuah negara. Penpreskripsian tidak rasional adalah satu fenomena global. Banyak kajian telah dilakukan untuk mendokumenkan pola penggunaan antibiotik dan hasilnya menunjukkan gejala preskripsi berlebihan, preskripsi drug berganda, salahguna drug, penggunaan drug mahal yang tidak perlu dan penggunaan antibiotik berlebihan adalah masalah yang lazim berkaitan pengunaan drug tidak rasional di kalangan para doktor.

Dengan mengumpulkan data dari 2,013 borang tuntutan yang dikeluarkan kepada pelajar Universiti Sains Malaysia, kajian ini bertujuan untuk meneliti perbezaan aspek berkenaan dengan penpreskripsian antibiotik kepada pelajar. Borang tuntutan dipilih secara tak rambang.

Hasil kajian menunjukkan diagnosis yang sering diberi terhadap pelajar Universiti Sains Malaysia ialah jangkitan saluran pernafasan atas (59.9%), gastroenteritis akut (5.8%) dan jangkitan saluran kencing (4.8%). Amoksisilin adalah antibiotik yang sering diberikan untuk jangkitan saluran penafasan atas (65.5%) dan jangkitan saluran kencing (52%). Bactrim® pula adalah antibiotik yang sering diberikan untuk gastroenteritis akut (57.2%). 48.1% keseluruhan antibiotik dipreskripsikan menggunakan jenama. 11.7% borang tuntutan antibiotik tidak mengikut Senarai Drug Perlu WHO dan 19.6% tidak mengikuti Garis Panduan Piawaian Rawatan Malaysia. Dari jumlah keseluruhan borang tuntutan, 93% tidak ditentukan dosnya, 59.8% tidak

ditulis bentuk dos, 72.9% tidak ditulis kekerapan dos dan 77.7% tidak ditulis tempoh rawatan. 1.4% antibiotik didapati mempunyai masalah kontraindikasi, 0.1% masalah duplikasi antibiotik dan 5.6% memberikan saling tindakan drug-drug.

Kesimpulan kajian ini menunjukkan pola penggunaan antibiotik dikalangan klinik panel U.S.M. mempunyai potensi masalah seperti kekurangan pemantauan, saling tindakan drug yang boleh membawa kesan buruk terhadap penjagaan pesakit dan perlunya mendokumentasikan hasil rawatan. Terdapat doktor yang tidak mengikuti Garis Panduan Piawaian Rawatan Malaysia dan Formulasi Drug. Garispanduan mestilah mudah diekses bagi memperbaiki aspek penggunaan drug secara rasional. Terdapat tiga perkara yang memerlukan tindakan lanjut untuk memperbaiki kualiti penjagaan kesihatan iaitu purata jumlah drug dalam setiap borang tuntutan, peratusan borang tuntutan yang mengandungi antibiotik dan peratusan antibiotik yang dipreskripsikan dengan nama generik.

ABSTRACT

Drug utilization study is important in establishing the status of drug use in a particular country, irrational prescribing is a global phenomenon. Many studies have been carried out to document antibiotic use patterns, and indicate that over prescribing, multiple drug prescribing, misuse of drugs, use of unnecessary expensive drugs and overuse of antibiotics are the most common problems of irrational drug use by prescribers.

By retrospectively recording data from 2,013 claim forms issued to students of Universiti Sains Malaysia during the period 1997, the study sets out to examine different aspects of prescribing antibiotics to students. The claim forms were selected non-randomly from the National Poison Center.

Results showed that the most frequent diagnosis given to USM's students were upper respiratory tract infection (59.9%), acute gastroenteritis (5.8%) and urinary tract infection (4.8%). Amoxycillin was the most common antibiotic given in cases of upper respiratory tract infections (65.5%) and urinary tract infections (52%), while Bactrim was the most common antibiotic given in cases of acute gastroenteritis (57.2%). The total numbers of brand name antibiotics prescribed were 48.1%. About 11.7% of the claim forms did not follow the WHO Essential Drug List and 19.6% of the antibiotic claim form did not follow the Malaysian Standard Treatment Guidelines. Of the total claim forms, 93% had unwritten dose, 59.8% had unwritten dosage form, 72.9% had unwritten frequency and 77.7% had unwritten duration. It was found that 1.4% of

antibiotics were contraindication, 0.1% of antibiotic duplicated and 5.6% having drug-drug interactions.

It was concluded in this study that current usage patterns of antibiotics in USM's panel clinic indicate some potential problems due to inadequate monitoring for drug interactions, a need to document outcome, some doctors not following the Malaysia Standard Treatment Guideline and drug formularies. Guideline should be readily accessible to improve rational drug use. The average number of drugs per claim forms, the percentage of claim forms with antibiotics prescribed and the percentage of generic antibiotics prescribed, are the three areas, which need further intervention to improve the quality of health care.

CHAPTER I

INTRODUCTION

1.1. Background

Drugs are being constantly developed which help to improve the quality as well as the life span, and if they are properly taken, they can actually reduce long-term hospitalization and other medical costs. With the advancement of medical science, large numbers of pharmaceutical preparations have been made available for human use. Drug therapy is becoming more complex. Many new prescription drugs have been approved every year; as a result, thousands of pages of complex drug information on these and other products are released every month.

Moreover, patients today are older and sicker. They need more potent and sophisticated drug therapy. Administering the wrong drug, strength, or dose; confusion over "look-alike" and "sound-alike" drugs; incorrect routes of administration; miscalculations; and errors in prescribing and transcription happen every day in every kind of health-care setting. The potential for adverse drug events and **medication error** is a reality, they occur in all parts of medication use system, of which prescribing and administration reportedly account for majority of the errors (Donald, 2000).

Every error is potentially tragic and costly in both human and economic terms, for patients and professionals alike. These lead to necessitating concern about their judicious use. The **irrational use** of drugs is a global problem affecting developing and developed countries alike. The misuse of drugs, which is widely prevalent, warrants constant monitoring, especially the antibiotics.

1.2. Brief history of antimicrobial agents

There are many different types of antimicrobial agents available today. By definition this would include anything that kills microorganisms. Discussed here are only antibiotics and antifungal agents.

Antibiotic refers to compounds isolated from one living organism that kill or inhibit the growth of other organisms. Antibiotics may have e.g., antibacterial, antifungal, antiviral, antiparasitic, or even anticancer activity. The term is loosely used as a synonym for more specific categories such as anticancer, antimicrobial, or antibacterial drug.

Antibiotics are still highly effective treatment for infection. There is no need for antibiotics unless there is bacterial infection. In many cases of infections such as flu, sore throat and cough, the patient recovers whether antibiotics are given or not. If they are used, they have little or no effect on the course of illness. Common cold and cough are caused by viruses and antibiotics do not fight viruses but only bacteria. Therefore, the doctor should only prescribe antibiotic when there is a secondary bacterial infection (Geoffry, 1994).

Since their discovery in the 1930s, antibiotics have made it possible to cure diseases caused by bacteria such as pneumonia, tuberculosis, and meningitis thus saving the lives of millions of people around the world. Antibiotics must be used wisely, because bacteria which are living organisms, always mutate in an effort to resist the drugs that can kill them. When antibiotics are used incorrectly, bacteria can adapt and become resistant. Antibiotics are then no longer useful in fighting them.

Antibiotic resistance is now a major public health issue. The correct use of these drugs is the best way to ensure that antibiotics remain useful in treating infections (Jacobson et al, 1995).

Antifungal agent is the drug that used mainly in the treatment and prophylaxis of fungal infections. They include the allylamines, several polyene macrolide antibiotics [including amphotericin and nystatin], other antifungal antibiotics [e.g. griseofulvin], imidazole derivatives [such as ketoconazole], triazole derivatives [such as fluconazole], some fatty acids [caprylic and propionic acid and their salts], and a number of other compounds among them are amorlfine, ciclopirox olamine, flucytosine, haloprogin, tolnaftate, and undecenoic acid and its salts.

1.3. Description of specific antimicrobial classes

The following discussion of antibiotics and chemotherapeutic organizes the antimicrobial agents based on their mode of action in bacterial cells.

1.3.1. Agent that interfere with cell wall formation (cell wall synthesis inhibitors)

Cell wall synthesis inhibitors generally inhibit some step in the synthesis of bacterial peptidoglycan. Generally they exert their selective toxicity against eubacteria because human cells lack cell walls.

Beta lactam antibiotics. Chemically, these antibiotics contain a 4-membered beta lactam ring. They are the products of two groups of fungi, *Penicillium* and *Cephalosporium* molds, and are correspondingly represented by the **penicillins** and **cephalosporins**.

The beta lactam antibiotics are stereochemically related to D-alanyl-D-alanine, which is a substrate for the last step in peptidoglycan synthesis, the final cross-linking between peptide side chains. Penicillins bind to and inhibit the carboxypeptidase and transpeptidase enzymes that are required for this step in peptidoglycan biosynthesis.

Beta lactam antibiotics are normally bactericidal and require that cells be actively growing in order to exert their toxicity. Different beta lactams differ in their spectrum of activity and their effect on Gram-negative rods, as well as their toxicity, stability in the human body, rate of clearance from blood, whether they can be taken orally, ability to cross the blood-brain barrier, and susceptibility to bacterial beta-lactamases.

1.3.1.1. Penicillin

a. Natural penicillins

Natural penicillins, such as **Penicillin G** or **Penicillin V**, are produced by fermentation of *Penicillium chrysogenum*. They are effective against streptococcus, gonococcus and staphylococcus, except where resistance has developed. They are considered narrow spectrum since they are not effective against Gram-negative rods.

b. Semi synthetic penicillins

Semi-synthetic penicillins first appeared in 1959. A mold produces the main part of the molecule (6-aminopenicillanic acid), which can be modified chemically by the addition of side chains. Many of these compounds have been developed to have distinct benefits or advantages over penicillin G, such as increased spectrum of activity (effectiveness against Gram-negative rods), resistance to penicillinase, effectiveness when administered orally, etc. **Amoxycillin** and **Ampicillin** have broadened spectra against Gram-negatives and are effective orally; **Methicillin** is penicillinase-resistant.

Although nontoxic, penicillins occasionally cause death when administered to persons who are allergic to them. In the U.S. there are 300 - 500 deaths annually due to penicillin allergy. In allergic individuals the beta lactam molecule attaches to a serum protein, which initiates an IgE-mediated inflammatory response.

c. Carboxypenicillins e.g. Carbenicillin & Ticarcillin

The first agent in this group was Carbenicillin. It is no longer in wide use because of the relative drawbacks including high sodium load predisposing to congestive heart failure and renal potassium wasting and an antiplatelet effect stemming from physical coating of the platelets. However, there is another derivative-Ticarcillin. It is still in use and the total dose required is lower. The major benefit to this group of penicillin antibiotics is the extended spectrum of activity against Gram-negative bacteria notably pseudomonas species as well as the anaerobes.

d. Uridopenicillins e.g. Mezlocillin, Azocillin, Piperacillin

The most recent development in the penicillin group is Uridopenicillins. These are now in common use due to their very broad spectrum. These antibiotics combine some of the good features of ampicillin (coverage of *Enterococci and Hemophilus species*) with the advantage of the Carboxypenicillins (good *Pseudomonas* and other Gram-negative bacterial coverage and good anaerobic coverage). However, resistance can be encountered due to beta-lactamases. Therefore, the Uridopenicillins are often combined with another agent such as an Aminoglycosides in serious infection.

1.3.1.2. Cephalosporins

Cephalolsporins are beta lactam antibiotics with a similar mode of action to penicillins that are produced by species of Cephalosporium. They have a low toxicity and a somewhat broader spectrum than natural penicillins. They are often used as penicillin substitutes, against Gram-negative bacteria, and in surgical prophylaxis. They are subject to degradation by some bacterial beta lactamases, but they tend to be resistant to beta-lactamases from *S. aureus.*

Table 1.1 Partial lists of cephalosporins antibiotics

First generation	Second generation	Third generation	Fourth generation
-cefazolin -cephapirin -cephalexin(oral) -cefadroxil(oral)	-cefoxitin -cefaclor(oral) -cefotetan -cefuroxime -cefamandole -cefonocid	-moxalactam -cefotaxime -cefoperazone -ceftriaxone -ceftazidime	-cefepim

First Generation

It is relatively broad-spectrum antibiotics. Primarily used as an effective antistaphylococcal agent. It covers skin flora and many Gram-negative bacteria as well.

Second Generation

Extends spectrum by including more Gram-negative bacilli. It's used primarily for the coverage of specific groups of organisms, example: cefoxitin is a good anaerobic drug and covers some anaerobes resistant to penicillin. It is also less toxic than clindamycin or chloramphenicol and is used in diabetic foot ulcers and nosocomial aspiration pneumonia where mixed Gram-positive and anaerobic bacteria are often encountered. Most second-generation compounds have some activity against indole-positive *Proteus, Enterobacter* , and *H.influenzae.*

Third Generation

It is a much broader Gram-negative spectrum antibiotic. It is often employed in cases of suspected etiology. Via chemical modification some have very long half-life (e.g. ceftriaxone) so the number of doses required per day is reduced.

Fourth generation

It is used in the treatment of complicated and uncomplicated urinary tract infection, skin infection caused by *streptococcus pyogenes*; and have activity against gram-negative organisms (Charles et al, 2001).

Disadvantages of cephalosporins (especially later generations)

The later generations are more expensive. Less staphylococcal coverage with 2nd and 3rd generations compared to 1st generation. Penicillins and cephalosporins both contain a beta-lactam ring. Organisms may become resistant to them via the action of a beta-lactamase enzyme.

1.3.1.3. Clavulanic acid

Clavulanic acid is a chemical sometimes added to a semisynthetic penicillin preparation. Thus, amoxycillin plus clavulanate is **clavamox** or **augmentin**. The clavulanate is not an antimicrobial agent. It inhibits beta lactamase enzymes and has given extended life to penicillinase-sensitive beta lactams.

1.3.1.4. Other agent that interfere with cell wall formation

Two other classes of beta lactams are the **carbapenems** and **monobactams**. The latter are particularly useful for the treatment of allergic individuals. A person who becomes allergic to penicillin usually becomes allergic to the cephalosporins and the carbapenems as well. Such individuals can still be treated with the monobactams, which are structurally different so as not to induce allergy.

Bacitracin is a polypeptide antibiotic produced by *Bacillus* species. It prevents cell wall growth by inhibiting the release of the muropeptide subunits of peptidoglycan from the lipid carrier molecule that carries the subunit to the outside of the membrane. Teichoic acid synthesis, which requires the same carrier, is also inhibited. Bacitracin has a high toxicity, which precludes its systemic use. It is present in many topical antibiotic preparations, and since the gut does not absorb it, it is given to "sterilize" the bowel prior to surgery.

Cycloserine inhibits the early stages of murein synthesis where D-alanyl-D-alanine is added to the growing peptide side chain. The antibiotic resembles D-alanine in spatial structure, and it competitively inhibits the racemase reaction that converts L-alanine to D-alanine and the synthetase reaction that joins two D-alanine molecules. The affinity of cycloserine for these enzymes is about a hundred times greater than that of D-alanine. Cycloserine enters bacterial cells by means of an active transport system for glycine and can reach a relatively high intracellular concentration. This concentrating effect, along with its high affinity for susceptible enzymes, enables cycloserine to function as a very effective antimicrobial agent. However, it is fairly toxic and has limited use as a secondary drug for tuberculosis.

Glycopeptides, such as the antibiotic **vancomycin**, appear to inhibit both transglycosylation and transpeptidation reactions during peptidoglycan assembly. They bind to the muropeptide subunit as it is transferred out of the cell cytoplasm and inhibit subsequent polymerization reactions. Vancomycin is not effective against Gram-negative bacteria because it cannot penetrate their outer membrane. However, it has become important in clinical usage for treatment of infections by strains of *Staphylococcus aureus* that are resistant to virtually all other antibiotics.

1.3.1.5. Major limitation of beta-lactam antibiotics

It is not toxic, but rather the fact that a significant portion of the population is allergic to them. Penicillin allergy should not contraindicate the administration of cephalosporins unless the reaction is of the immediate type (angioneurotic edema, or urticaria).

1.3.2 Protein inhibitor class of antibiotics (Protein synthesis inhibitors)

Many therapeutically useful antibiotics owe their action to inhibition of some steps in the complex process of protein synthesis. Their attack is always at one of the events occurring on the ribosome and never at the stage of amino acid activation or attachment to a particular tRNA. Most have an affinity or specificity for 70S (as opposed to 80S) ribosomes, and they achieve their selective toxicity in this manner. The most important antibiotics with this mode of action are the **tetracyclines**, **chloramphenicol**, the **macrolides** (e.g. erythromycin) and the **aminoglycosides** (e.g. streptomycin).

1.3.2.1. Aminoglycosides

The aminoglycosides are products of *Streptomyces* species and are represented by **streptomycin**, **kanamycin**, **tobramycin** and **gentamicin**. These antibiotics exert their activity by binding to bacterial ribosomes and preventing the initiation of protein synthesis.

Streptomycin binds to 30S subunit of the bacterial ribosome, specifically to the S12 protein, which is involved in the initiation of protein synthesis. Experimentally, streptomycin has been shown to prevent the initiation of protein synthesis by blocking the binding of initiator N-formylmethionine tRNA to the ribosome. It also prevents the normal dissociation of ribosomes into their subunits, leaving them mainly in their 70S form and preventing the formation of polysomes. The overall effect of streptomycin seems to be one of distorting the ribosome so that it no longer can carry out its normal functions. This evidently accounts for its antibacterial activity but does not explain its bactericidal effects, which distinguishes streptomycin and other aminoglycosides from most other protein synthesis inhibitors.

Kanamycin and **tobramycin** have been reported to bind to the ribosomal 30S subunit and to prevent it from joining to the 50S subunit during protein synthesis. They may have a bactericidal effect because this leads to cytoplasmic accumulation of dissociated 30S subunits, which is apparently lethal to the cells.

Aminoglycosides have been used against a wide variety of bacterial infections caused by Gram-positive and Gram-negative bacteria. Streptomycin has been used extensively as a primary drug in the treatment of tuberculosis. **Gentamicin** (a mixture of 3 components) is active against many strains of Gram-positive and Gram-negative bacteria, including some strains of *Pseudomonas aeruginosa*. **Kanamycin** (a complex of three antibiotics, A, B and C) is active at low concentrations against many Gram-positive bacteria, including penicillin-resistant staphylococci. **Gentamicin** and **Tobramycin** are mainstays for treatment of *Pseudomonas* infections. An unfortunate side effect of aminoglycosides has tended to restrict their usage: prolonged use is known to impair kidney function and cause damage to the auditory nerves leading to deafness.

1.3.2.2. Aminocyclitol

Spectinomycin is related to aminoglycosides. It is used to treat *penicillin-resistant Gonorrhea.*

1.3.2.3. Chloramphenicol

Chloramphenicol is a protein synthesis inhibitor has a broad spectrum of activity but it exerts a bacteriostatic effect. It is effective against intracellular parasites such as the rickettsiae. Unfortunately, aplastic anemia, which is dose-related, develops in a small proportion (1/50,000) of patients. Chloramphenicol was originally discovered and purified from the fermentation of a *Streptomyces*, but currently it is produced entirely by chemical synthesis. Chloramphenicol inhibits the bacterial enzyme

peptidyl transferase, thereby preventing the growth of the polypeptide chain during protein synthesis.

Chloramphenicol is entirely selective for 70S ribosomes and does not affect 80S ribosomes. Its unfortunate toxicity towards the small proportion of patients who receive it is in no way related to its effect on bacterial protein synthesis. However, since mitochondria probably originated from procaryotic cells and have 70S ribosomes, they are subject to inhibition by some of the protein synthesis inhibitors including chloroamphenicol. This likely explains the toxicity of chloramphenicol. The eukaryotic cells most likely to be inhibited by chloramphenicol are those undergoing rapid multiplication, thereby rapidly synthesizing mitochondria. Such cells include the blood forming cells of the bone marrow, the inhibition of which could present as aplastic anemia. Chloramphenicol was once a highly prescribed antibiotic and a number of deaths from anemia occurred before its use was curtailed. Now it is seldom used in human medicine except in life-threatening situations (e.g. typhoid fever).

1.3.2.4. Clindamycin and Lincomycin

Lincomycin and clindamycin are a miscellaneous group of protein synthesis inhibitors with activity similar to the macrolides. **Lincomycin** has activity against Gram-positive bacteria and some Gram-negative bacteria (*Neisseria, H. influenzae*). **Clindamycin** is a derivative of lincomycin, with the same range of antimicrobial activity, but it is considered more effective. It is frequently used as a penicillin substitute and is effective against Gram-negative anaerobes (e.g. *Bacteroides*).

1.3.2.5. Macrolide

The macrolide family of antibiotics is characterized by structures that contain large lactone rings linked through glycoside bonds with amino sugars. The most important members of the group are **erythromycin** and **oleandomycin**. **Erythromycin** is active against most Gram-positive bacteria, *Neisseria, Legionella* and *Haemophilus,* but not against the *Enterobacteriaceae*. Macrolides inhibit bacterial protein synthesis by binding to the 50S ribosomal subunit. Binding inhibits elongation of the protein by peptidyl transferase or prevents translocation of the ribosome or both. Macrolides are bacteriostatic for most bacteria but are cidal for a few Gram-positive bacteria.

1.3.2.6. Tetracyclines

The tetracyclines consist of eight related antibiotics, which are all natural products of *Streptomyces*, although some can now be produced semi-synthetically or synthetically. **Tetracycline, chlortetracycline** and **doxycycline** are the best known. The tetracyclines are broad-spectrum antibiotics with a wide range of activity against both Gram-positive and Gram-negative bacteria. *Pseudomonas aeruginosa* is less sensitive but is generally susceptible to tetracycline concentrations that are obtainable in the bladder. The tetracyclines act by blocking the binding of aminoacyl tRNA to the A site on the ribosome.

Tetracyclines inhibit protein synthesis on isolated 70S or 80S (eukaryotic) ribosomes, and in both cases, their effect is on the small ribosomal subunit. However, most bacteria possess an active transport system for tetracycline that will allow intracellular accumulation of the antibiotic at concentrations 50 times as great as that in the medium. This greatly enhances its antibacterial effectiveness and accounts for its specificity of action, since an effective concentration cannot be accumulated in animal

cells. Thus a blood level of tetracycline, which is harmless to animal tissues, can halt protein synthesis in invading bacteria.

The tetracyclines have a remarkably low toxicity and minimal side effects when taken by animals. The combination of their broad spectrum and low toxicity has led to their overuse and misuse by the medical community and the widespread development of resistance has reduced their effectiveness. Nonetheless, tetracyclines still have some important uses, such as the use of **doxycycline** in the treatment of Lyme disease.

Some newly discovered members of the tetracycline family (e.g. chelocardin) have been shown to act by inserting into the bacterial membrane, not by inhibiting protein synthesis.

1.3.3. Antibiotics that affect cell membranes (cell membrane inhibitors)

These antibiotics disorganize the structure or inhibit the function of bacterial membranes. The integrity of the cytoplasmic and outer membranes is vital to bacteria, and compounds that disorganize the membranes rapidly kill the cells. However, due to the similarities in phospholipids in eubacterial and eukaryotic membranes, this action is rarely specific enough to permit these compounds to be used systemically. The only antibacterial antibiotic of clinical importance that acts by this mechanism is **polymyxin**, produced by *Bacillus polymyxis*. Polymyxin is effective mainly against Gram-negative bacteria and is usually limited to topical usage. Polymyxin binds to membrane phospholipids and thereby interferes with membrane function. Polymyxin is occasionally given for urinary tract infections caused by *Pseudomonas* strains that are gentamicin, carbenicillin and tobramycin resistant. The balance between effectiveness and damage to the kidney and other organs is

dangerously close, and the drug should only be given under close supervision in the hospital.

1.3.4. Antibiotics affecting nucleic acids

Some antibiotics and chemotherapeutic agents affect the synthesis of DNA or RNA, or can bind to DNA or RNA so that their messages cannot be read. Either case, of course, can block the growth of cells. The majority of these drugs are unselective, however, and affect animal cells and bacterial cells alike and therefore have no therapeutic application. Two nucleic acid synthesis inhibitors, which have selective activity against procaryotes, and some medical utility are the **quinolones** and **rifamycins**.

Nalidixic acid is a synthetic chemotherapeutic agent, which has activity mainly against Gram-negative bacteria. Nalidixic acid belongs to a group of compounds called quinolones. Nalidixic acid is a bactericidal agent that binds to the DNA gyrase enzyme (topoisomerase), which is essential for DNA replication and allows supercoils to be relaxed and reformed. Binding of the drug inhibits DNA gyrase activity.

Some quinolones penetrate macrophages and neutrophils better than most antibiotics and are thus useful in treatment of infections caused by intracellular parasites. However, the main use of nalidixic acid is in treatment of lower urinary tract infections (UTI). The compound is unusual in that it is effective against several types of Gram-negative bacteria such as *E. coli, Enterobacter aerogenes, K. pneumoniae* and *Proteus* species, which are common, causes of UTI. It is not usually effective against *Pseudomonas aeruginosa*, and Gram-positive bacteria are resistant.

Some quinolones have a broadened spectrum against Gram-positive bacteria. The **fluoroquinolone**, Cipro. (ciprofloxacin) was recently touted as the drug of choice for treatment and prophylaxis of anthrax, which is caused by a Gram-positive bacillus.

The **rifamycins** are a comparatively new group of antibiotics, also the products of *Streptomyces*. Rifampicin is a semisynthetic derivative of **rifamycin** that is active against Gram-positive bacteria (including *Mycobacterium tuberculosis*) and some Gram-negative bacteria. **Rifampicin** acts quite specifically on the bacterial RNA polymerase and is inactive towards DNA polymerase or RNA polymerase from animal cells. The antibiotic binds to the beta subunit of the polymerase and apparently blocks the entry of the first nucleotide, which is necessary to activate the polymerase, thereby blocking mRNA synthesis. It has been found to have greater bactericidal effect against *M. tuberculosis* than other anti-tuberculosis drugs, and it has largely replaced isoniazid as one of the front-line drugs used to treat the disease, especially when isoniazid resistance is indicated. It is effective orally and penetrates the cerebrospinal fluid so it is useful for treatment of bacterial meningitis.

1.3.4. Competitive inhibitors

Many of the synthetic chemotherapeutic agents are **competitive inhibitors** of essential metabolites or growth factors that are needed in bacterial metabolism. Hence, these types of antimicrobial agents are sometimes referred to as **anti-metabolites** or **growth factor analogs**, since they are designed to specifically inhibit an essential metabolic pathway in the bacterial pathogen. At a chemical level, competitive inhibitors are structurally similar to a bacterial growth factor or metabolite, but they do not fulfill their metabolic function in the cell. Some are bacteriostatic and some are

bactericidal. Their selective toxicity is based on the premise that the bacterial pathway does not occur in the host.

Sulfonamides were introduced as chemotherapeutic agents by Domagk in 1935, who showed that one of these compounds (prontosil) had the effect of curing mice with infections caused by beta-hemolytic streptococci. Chemical modifications of the compound sulfanilamide gave compounds with even higher and broader antibacterial activity. The resulting sulfonamides have broadly similar antibacterial activity, but differ widely in their pharmacological actions. Bacteria, which are almost always sensitive to the sulfonamides, include *Streptococcus pneumoniae*, beta-hemolytic streptococci and *E. coli*. The sulfonamides have been extremely useful in the treatment of uncomplicated UTI caused by *E. coli*, and in the treatment of meningococcal meningitis (because they cross the blood-brain barrier).

The sulfonamides (e.g. **Gantrisin**) and **Trimethoprim** are inhibitors of the bacterial enzymes required for the synthesis of tetrahydrofolic acid (THF), the vitamin form of folic acid essential for 1-carbon transfer reactions. Sulfonamides are structurally similar to para aminobenzoic acid (PABA), the substrate for the first enzyme in the THF pathway, and they competitively inhibit that step. Trimethoprim is structurally similar to dihydrofolate and competitively inhibits the second step in THF synthesis mediated by the DHF reductase. Animal cells do not synthesize their own folic acid but obtain it in a preformed fashion as a vitamin. Since animals do not make folic acid, they are not affected by these drugs, which achieve their selective toxicity for bacteria on this basis.

Three additional synthetic chemotherapeutic agents have been used in the treatment of tuberculosis: **(INH)**, **paraaminosalicylic acid (PAS)**, and **ethambutol**. The usual strategy in the treatment of tuberculosis has been to administer a single

antibiotic (historically streptomycin, but now, most commonly, rifampicin is given) in conjunction with INH and ethambutol. Since the tubercle bacillus rapidly develops resistance to the antibiotic, ethambutol and INH are given to prevent outgrowth of a resistant strain. It must also be pointed out that the tubercle bacillus rapidly develops resistance to ethambutol and INH if either drug is used alone. Ethambutol inhibits incorporation of mycolic acids into the mycobacterial cell wall. Isoniazid has been reported to inhibit mycolic acid synthesis in mycobacteria and since it is an analog of pyridoxine (Vitamin B6) it may inhibit pyridoxine-catalyzed reactions as well. Isoniazid is activated by a mycobacterial peroxidase enzyme and destroys several targets in the cell. PAS is an anti-folate, similar in activity to the sulfonamides. PAS was once a primary anti-tuberculosis drug, but now it is a secondary agent, having been largely replaced by ethambutol.

1.4. Problem with antibiotic use

The concerns regarding inappropriate antibiotic use can be divided into four areas: efficacy, toxicity, cost and resistance. Inappropriate use of antibiotic can be due to:-(a) antibiotic use where no infection is present, e.g. continuation of peri-operative prophylaxis for more than 24 hours after a clean surgery; (b) infection which is not amenable to antibiotic therapy, e.g. antibiotics prescribed for viral upper respiratory tract infection; (c) the wrong drug for the causative organism, e.g. the use of broad spectrum anti-Gram negative agents for community acquired pneumonia; (d) the wrong dose or duration of therapy. Such inappropriate use has a measurable effect on the therapeutic efficacy. For example, one study showed that mortality in gram-negative septicemia is doubled when inappropriate empiric agents were used (Kreger et al, 1980). Since most initial antibiotic therapy is empiric, any attempt at improving the use must

tackle prescribing habits, with particular emphasis on the guidelines of therapy based on the clinical criteria.

Inappropriate antibiotic used exposes patients to the risk of drug toxicity, while giving little or no therapeutic advantage. Antibiotics are often considered relatively safe and yet direct or indirect side effects of their use are not infrequent and may be life-threatening. Allergic reactions, particularly to beta-lactam agents are well recognized and have been described in reaction to antibiotic residues in food (Barragry, 1994). Life threatening side effects may occur from the use of antibiotics for apparently simple infections. It is estimated that eight people per year in UK die from side effects of co-trimoxazole usage in the community (Robert and Edmond, 1998). Indirect side effects are often overlooked, especially as they may occur sometime after the antibiotic has been given. These include drug interactions (such as interference of antibiotic with anti-coagulant therapy and erythromycin with antihistamine) (BNF, 1998), side effects associated with the administration of antibiotics (such as intravenous cannula infection) and super-infection (such as candidiasis and pseudomembranous colitis). Each of these may have a greater morbidity, and indeed mortality, than the initial infection for which the antibiotic was prescribed (Kunin et al, 1993).

The medical benefit of antibiotics does not come cheap. In the hospital setting, in United States up to fifty percent of population receives one antibiotic during their hospital stay, with surgical prophylaxis according for thirty percent of this. The financial cost of this can be considerable. The antimicrobial bill for our own institution is approximately IR£800,000 per annum. This represents the acquisition costs of the drugs and does not include indirect costs (consumables, personnel, adverse effects etc.), which may far outweigh the cost of the individual drugs. Given that some 50% of antibiotic prescriptions may be inappropriate, it is clear that major cost savings can be

realized through more judicious antibiotic prescribing. Similar costs are found in general practice where IR£10,472,854 was spent on antimicrobials in the GMS alone in 1993 (the last year for which statistics are available) (Robert and Edmond, 1998).

The first penicillin resistant isolate of *staphylococcus aureus* was described only two years after the introduction of penicillin. Within a decade, 90% of isolates were penicillin resistant. This pattern of antibiotic discovery and introduction, followed by exuberant use and rapid emergence of resistance has subsequently been repeated with each new class of antibiotics introduced. Bacteria can so rapidly develop resistance due to two major evolutionary advantages. Firstly, bacteria have been in existence for some 3.8 billion years and resistance mechanisms have evolved over this time as a protective mechanism against naturally occurring compounds produced by other microorganisms. In addition, they have an extremely rapid generation time and can freely exchange genetic material encoding resistance, not only between other species but also between genera. The vast quantities of antibiotics used in both human and veterinary medicine, has lead to emergence of infection due to virtually untreatable bacteria. Multiple drug resistant tuberculosis is already widespread in parts of Southern Europe and has recently caused outbreaks in two hospitals in London (Hiramatsu et al, 1997).

Anti-infectives are vital drugs, but they are over-prescribed and over-used in the treatment of minor disorder such as simple diarrhea, cough and colds. When antibiotics are used too often in sub-optimal dosages, bacteria become resistant to them. The result is treatment failure where patient continue to suffer from serious infections despite taking the medication (Mohamed I, 1999).

Drugs prescribed are in no way beneficial to the patient's management if there are some negative interactions among the various agent prescribed, over prescribed, under prescribed or prescribed in the wrong dosage schedule.

How does one ensure that good drugs are not badly used, misused or even abused? How can drugs be used rationally as intended? What is **rational use** of drugs? What does rational mean?

1.5. Rational use of drug

> *"Rational use of drugs requires that patients receive medications appropriate to their clinical needs, in doses that meet their own individual requirements for an adequate period of time, and the lowest cost to them and their community* (WHO, 1985).

These requirements will be fulfilled if the process of prescribing is appropriately followed. This will include steps in defining patient's problems (or diagnosis); in defining effective and safe treatments (drugs and non-drugs); in selecting appropriate drugs, dosage and duration; in writing a prescription; in giving patients adequate information; and in planning to evaluate treatment responses. The definition implies that rational use of drugs; especially rational prescribing should meet certain criteria as follows (Ross et al, 1992):

Appropriate indication. The decision to prescribe drug(s) is entirely based on medical rationale and that drug therapy is an effective and safe treatment.

Appropriate drug. The selection of drugs is based on efficacy, safety, suitability and cost considerations.

Appropriate patient. No contraindications exist and the likelihood of adverse reactions is minimal, and the drug is acceptable to the patient.

Appropriate information. Patients should be provided with relevant, accurate, important and clear information regarding his or her condition and the medication(s) that are prescribed.

Appropriate monitoring. The anticipated and unexpected effects of medications should be appropriately monitored (Vance, 1986).

Unfortunately, in the real world, prescribing patterns do not always conform to these criteria and can be classified as inappropriate or irrational prescribing. Irrational prescribing may be regarded as "pathological" prescribing, where the above-mentioned criteria are not fulfilled. Common patterns of irrational prescribing, may therefore be manifested in the following forms:

1. The use of drugs when no drug therapy is indicated, e.g., antibiotics for viral upper respiratory infections,
2. The use of the wrong drug for a specific condition requiring drug therapy, e.g., tetracycline in childhood diarrhea requiring oral rehydration salt (ORS),
3. The use of drugs with doubtful/unproven efficacy, e.g., the use of antimotility agents in acute diarrhea,
4. The use of drugs of uncertain safety status, e.g., use of dipyrone,
5. Failure to provide available, safe, and effective drugs, e.g., failure to vaccinate against measles or tetanus, failure to prescribe ORS for acute diarrhea,
6. The use of correct drugs with incorrect administration, dosages, and duration, e.g., the use of IV metronidazole when suppositories or oral formulations would be appropriate.

7. The use of unnecessarily expensive drugs, e.g., the use of a third generation, broad spectrum antimicrobial when a first-line, narrow spectrum, agent is indicated.

Some examples of commonly encountered inappropriate prescribing practices in many health care settings include (Avorn and Harvey, 1987):

1. Overuse of antibiotics and antidiarrheals for non-specific childhood diarrhea,
2. Multiple drug prescriptions, prescribe unnecessary drugs to counteract or augment drugs already prescribed, and
3. Excessive use of antibiotics in treating minor respiratory tract infection.

The drug use system is complex and varies from country to country. Drugs may be imported or manufactured locally. The drugs may be used in hospitals or health centers, by private practitioners and often in a pharmacyor drug shop where OTC preparations are sold. In some countries all drugs are available over the counter! Another problem among the public includes a very wide range of people with differing knowledge, beliefs and attitudes about medicines.

1.5.1. Factors underlying irrational use of drugs

There are many different factors that affect the irrational use of drugs. In addition, different cultures view drugs in different ways, and this can affect the way drugs are used. The major forces can be categorized as those deriving from patients, prescribers, the workplace, the supply system including industry influences, regulation, drug information and misinformation, and combinations of these factors (Ross- Degnan et al, 1992).

Table 1.2 Factors affecting irrational use of drug

1-Patients: drug misinformation	Due to the misleading beliefs of patient and patient demands/expectations
2-Prescribers: lack of education and training	Due to inappropriate role models, lack of objective drug information, generalization of limited experience and misleading beliefs about drugs efficacy
3-Workplace: heavy patient load	Due to pressure to prescribe, lack of adequate lab capacity and insufficient staffing
4-Drug Supply System: unreliable suppliers	Due to drug shortages and expired drugs supplied
5-Drug Regulation: non-essential drugs available	Due to non-formal prescribers and lack of regulation enforcement
6-Industry: promotional activities	Due to misleading claims

1.5.2. Impact of inappropriate use of drugs

The impact of this irrational use of drugs can be seen in many ways (Avorn and Harvey, 1987):

1. Reduction in the quality of drug therapy leading to increased morbidity and mortality,
2. Waste of resources leading to reduced availability of other vital drugs and increased costs,
3. Increased risk of unwanted effects such as adverse drug reactions and the emergence of drug resistance, e.g., malaria or multiple drugs resistant tuberculosis,
4. Psychosocial impacts, such as when patients come to believe that there is "a pill for every ill". This may cause an apparent increased demand for drugs.

The government of Malaysia has adopted the primary health care approach as long –term strategy for providing health care to all residents of the country. Primary

health care centers provide facilities for disease prevention and treatment, promotion of health and rehabilitation (MOH, 1993).

Several local regulatory bodies have been formed to ensure that drug availability and prescribing in the district conform to the highest contemporary standards. Antibiotic Control Committee was formed to provide guidelines to practicing physicians about the use and abuse of antibiotics. The Committee is responsible for analyzing the pattern of antibiotic prescriptions and preparing guidelines for antibiotic use. The Committee produced guidelines related to antibiotics that were circulated to all physicians in the district (Marr et al, 1988).

The guidelines emphasized the following aspects:

1. The presence of up-to-date information about all antibiotics in each primary health-care center and hospital.
2. Methods and strategies for choosing appropriate antibiotics for a specific disease condition.
3. The establishment of antibiotics subcommittees in each health-care facility for auditing antibiotics use. The information package contained articles about the use and abuse of antibiotics. Worldwide meetings were organized with the physicians of the districts to discuss the states of antibiotics and the details of the guidelines.

1.6. The rationale prescription (i.e. the right to prescribe)

The rights to prescription writing must ensure the patient's five rights (i) the right drug, (ii) the right dose, (iii) by the right route, (iv) to the right patient and (v) at the right time. Illegible handwriting and misinterpretation of prescriptions and medication orders are widely recognized causes of prescription error. The medicines