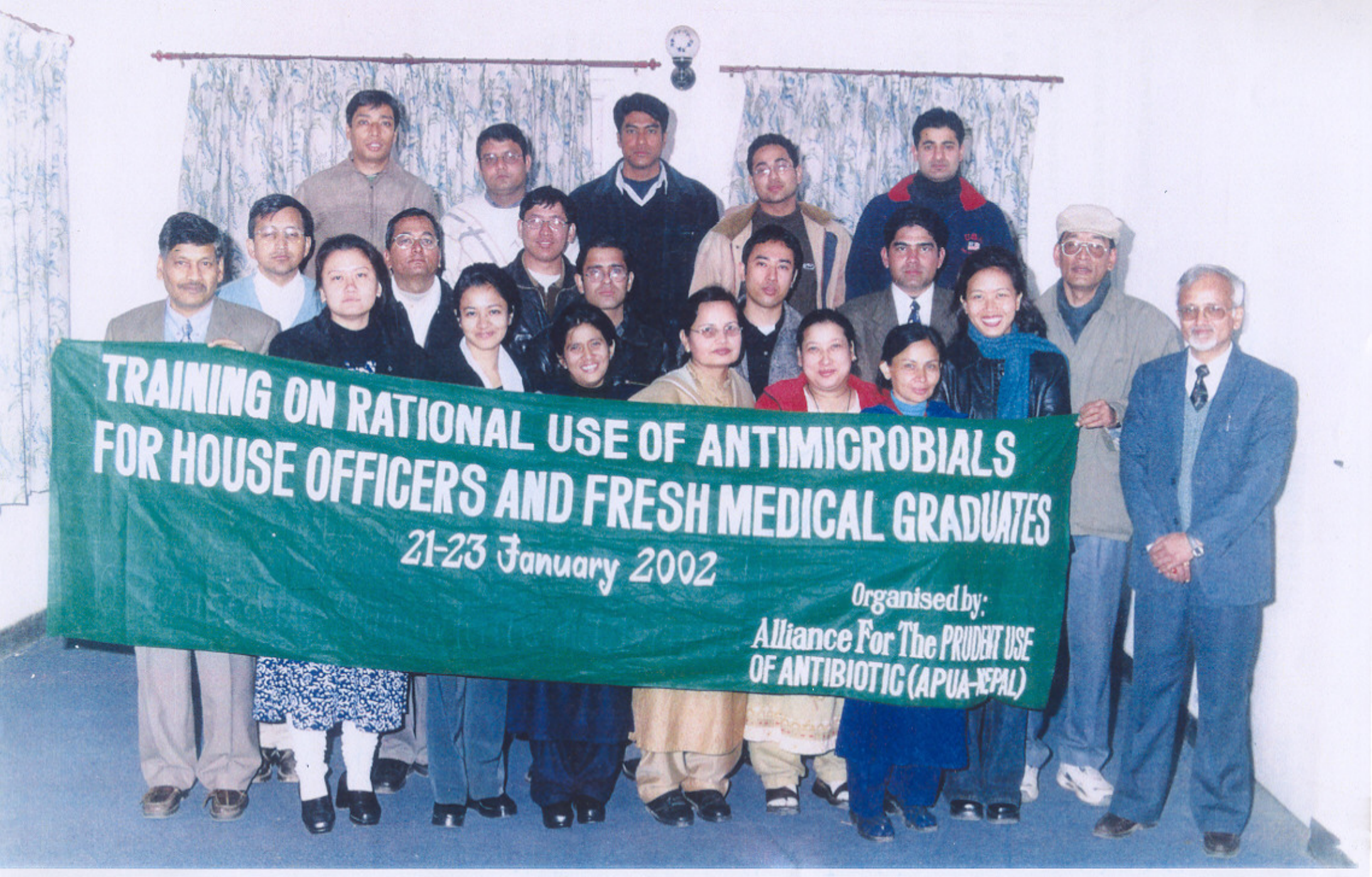
Training Workshop on Rational Use of Anti-microbials for House Officers and Fresh Medical Graduates

Alliance for the Prudent Use of Antibiotics (APUA)-Nepal
GPO Box 8975, EPC 1313, Kathmandu, Nepal
January 2002


TRAINING ON RATIONAL USE OF ANTIMICROBIALS
FOR HOUSE OFFICERS AND FRESH MEDICAL GRADUATES
21-23 January 2002
Organised by:
Alliance For The PRUDENT USE
OF ANTIBIOTIC (APUA-NEPAL)

Contents

Acknowledgement

We would like to thank all the hospitals and medical colleges authority for sending participants for the training. We are grateful to Department of Drug Administration for availing training hall for the workshop.

We would like to express our sincere thanks to all trainers for sparing their precious time in making the training successful and also to the trainees for their cooperation in answering our pre and post evaluation questionnaires.

We are grateful to Nepal Health Research Council (NHRC), in particular, Dr. Kamal Gyawali, the then Member secretary for providing financial support for the training workshop. Last but not the least, we would like to thank Mr. Arjun R. Pandey of Institute of Medicine for statistical work.

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Executive Summary

A training workshop on "Rational Use of Anti-microbials for House Officers and Fresh Medical Graduates" was developed and conducted. Participants were from 9 hospitals and medical colleges of Kathmandu Valley. The training was organized from 21-23 January 2002 at the Department of Drug Administration, Bijulibajar, Kathmandu. Total of 11 sessions were conducted by resource persons from different organizations/ institutions/ expertise.

The participants were evaluated before and after the training to assess their knowledge.

The important findings were a significant increase in knowledge on factors contributing to the emergence of drug resistant microbes, development of resistance, multi-drug resistance and communicable disease from animal food products.

1. Background

Antibiotics are one of the most important therapeutic discoveries in the history of medicine. They have revolutionized our ability to decrease death and disease from infectious microorganisms. Its effectiveness in killing microorganisms has led to their misuse and overuse. Due to its widespread use, bacteria responded with different ways to resist the killing power of antibiotics. Highly effective antibiotics are becoming less effective in killing those once highly susceptible organisms. Resistant to antibiotics doesn't remain within those particular bacteria but is readily transferred to other microbes. The situation is becoming dangerous everyday. To curb development of antimicrobial resistance and its spread, one of the important weapons is to use antibiotics judiciously.

In such background, training workshop on rational use of anti-microbials becomes highly significant in orders to improve prescribing, dispensing and use. Training to health care professionals and to the consumer is of paramount value to achieve the goal.

Alliance for the Prudent Use of Antibiotics (APUA)- Nepal chapter conducted 3 days training workshop on rational use of anti-microbials to the house officers and fresh medical graduates with the financial support from the Nepal Health Research Council (NHRC).

2. Course Objectives

The objectives of the training workshop were:

1. To impart and sensitize about the extent of use of antibiotics.
2. To describe principles of antimicrobial selection.
3. To describe the mechanism of resistance and cross-resistance.
4. To explain the significance of microbiological diagnosis for the treatment of infectious diseases and prevention of antimicrobial resistance.
5. To list the conditions for prophylactic antibiotic use.
6. To describe various measures to curb antimicrobial resistance.
7. To evaluate participant's knowledge on prudent use of antibiotics pre and post training.

3. Methodology

3.1 Selection of Participants

Fresh medical graduates and house officers from 9 hospitals and medical colleges were selected for the training workshop. Total of 19 participants took part in the training.

3.2 Training Methods and Contents

Lectures and discussions were used in the training workshop. The topics included:

1. Principles of anti-microbial selection and use – host factor; host defense mechanism

2. Principles of anti-microbial selection and use-pharmacokinetic, pharmacodynamic and pharmacogenetic factors
3. Science of AMR – definition, resistance mechanism, transfer resistance (cross resistance), and value of microbiological diagnosis
4. Epidemiology of infectious disease: Disease prevalence
5. EHP (USAID/MOH) program on prevention and control of vector borne diseases in Nepal
6. Regulatory measures
7. Use of two or more antibiotics, advantages and disadvantages of use of multiple antibiotics
8. Use of anti-microbials in children.
9. Use of anti-microbials in pregnancy
10. Prophylactic use of anti-microbials, antimicrobials in elderly
11. Public health challenges due to AMR

The trainers were general physicians, clinical pharmacologists, pediatrician, microbiologist, pharmacists, gynecologist, and veterinarian from different governmental and non-governmental institutions. The total duration of training was 3 days.

3. 3 Evaluation of the training

The training was evaluated before and after the training to assess participant' s knowledge on prudent use of antibiotics.

3.4 Coding

The answers were coded correct or incorrect; excellent, good, fair or poor based on defined indicators.

3.5 Data Analysis

The data were analyzed manually. Test of significance was done by chi-square test at 95% confidence limit.

4. Results

The results of knowledge on prudent use of antibiotics before and after the training are as follows:

I. Knowledge on antimicrobial resistance

Response	Pre	Post
	%	%
Correct	55.6	88.9†
Incorrect	44.4	11.1
No response	0.0	0.0

Correct response based on the following:

- **It is the microbes (bacteria, virus, fungus or protozoa) that is resistant, not the drug, nor the patient.**

† There was no significant difference in correct response.

II. Knowledge on factors contributing to the emergence of drug resistant microbes

Response	Pre %	Post %
Good	22.2	83.3‡
Fair	38.9	11.1
Poor	33.3	5.6
No response	5.6	0.0

Responses were based on the following:

- **Wrong choice of drug**
- **Incorrect dosage**
- **Incorrect duration of treatment**
- **Poor compliance with the treatment**
- **Use of low quality of drug**

Excellent: Any four
Good: Any two
Fair: Any one
Poor: None

‡ There was significant difference in response.

III. Knowledge on the development of resistance

Response	Pre %	Post %
Good	5.6	77.8‡
Fair	61.0	11.1
Poor	27.8	11.1
No response	5.6	0.0

Grading based on the following:

- **Mutation**
- **Acquisition from other bacteria of resistant genes**

Good: Two
Fair: Any one
Poor: None

‡ There was significant difference in response.

IV. Knowledge about multi-drug resistance

Response	Pre %	Post %
Correct	50.0	88.9‡
Incorrect	50.0	11.1
No response	0.0	0.0

Correct response based on:

- **Resistant of microbes to more than two anti-microbials**

‡ There was significant difference in response.

V. Knowledge on rapid development of anti-microbial resistance.

Response	Pre %	Post %
Good	0.0	22.2
Fair	11.1	5.6
Poor	88.9	72.2
No response	0.0	0.0

Response was based on the following:

- **Microbes multiply very rapidly**
- **Microbes spread readily from person to person**

Good: Two
Fair: Any one
Poor: None

VI. Knowledge on strategies to contain antimicrobial resistance.

Response	Pre %	Post %
Good	0.0	0.0
Fair	5.6	0.0
Poor	77.8	100.0
No response	16.6	0.0

Response were based on the following:

- **Curb emergence of resistance**
- **Curb spread of resistance**

Good: Two
Fair: Any one
Poor: None

VII. Knowledge on infection control practices.

Response	Pre %	Post %
Good	0.0	72.2
Fair	38.9	0.0
Poor	61.1	27.8
No response	0.0	0.0

Responses were based on the following:

- **Hand washing**
- **Changing gloves before and after contact with the patients**

Good: Two
Fair: Any one
Poor: None

VIII. Knowledge on anti-microbials not to be used in pregnancy.

Response	Pre %	Post %
Good	27.8	33.3†
Fair	72.2	66.7
Poor	0.0	0.0
No response	0.0	0.0

Responses were based on the following:

- **Tetracyclines**
- **Sulphonamides**
- **Quinolones**
- **Primaquin**
- **Aminoglycosides**
- **Chloramphenicol**
- **Co-trimoxazole**
- **Griseofulvin**
- **Ketoconazole**
- **Mefloquine**
- **Pyimethamine**
- **Tinidazole**

Excellent: Any ten
Good: Five to nine
Fair: One to four
Poor: None

† **There was no significant difference in response.**

5. Conclusion

The training workshop was effective in improving the knowledge on the prudent use of antibiotics.

It is expected that the increased knowledge on the prudent use of antibiotics will improve in their prescribing habit as well as decrease the influences of various external factors.

6. Recommendations

1. The duration of the training should be extended- ideally 1 week.
2. The training should be regular and extended to more prescribers. It should also be conducted on regional basis.
3. The national antibiotic guidelines should be developed in order to curb antimicrobial resistance.

Annex 1

The Principles of Antimicrobial Selection and Use. Host Defense against Infection.

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The principles are:
Regimens for therapeutic antimicrobial use should be optimized using current pharmacological information and principles.

Use narrow spectrum antimicrobials whenever appropriate

Utilize culture and susceptibility results to aid in the selection of antimicrobials when clinically relevant.

Therapeutic antimicrobial use should be confined to appropriate clinical indications. Inappropriate use such as for uncomplicated viral infections should be avoided. Therapeutic exposure to antimicrobials should be minimized by treating only for as long as needed for the desired medical response.

Minimize environmental contamination with antimicrobials whenever possible.

Preventive strategies, such as appropriate hygiene, routine health monitoring, and immunizations should be emphasized.

Accurate records of treatment and outcome should be used to evaluate therapeutic regimens.

General Rules of Antimicrobial therapy

1. Choice of Drug
2. Pharmacokinetic Considerations
3. Administration of Drug
4. Duration of Treatment
5. Antibacterial Combinations
6. Problems Created by Misuse

1. Choice of Drug

Patient characteristics
Cost
Maximize benefit/risk ration
Ideal – bacteriologic diagnosis
Sensitivity test
Best guess

Mixed infections
Life-threatening – combinations and broad spectrum till pathogens identified
Use narrow spectrum possible
Use bactericidal drugs if possible
Antimicrobial sensitivity patterns
Routine monitoring aids local ad hoc choices
Variation by locale published tables, but represent national or general sensitivities
Prophylaxis and Viral Infections
Target prophylaxis: Varies with drug
Piperacillin < ampicillin
Broad-spectrum drugs > narrow spectrum

Acquire Cross- Resistance Among Anti-microbials

Also called parallel resistance
Difference among members of same group of drugs
Shift to which antimicrobial if resistance?
Sensitivity testing – prototype drug?
Cross resistance common
- tetracyclines
- sulfonamids
- neomycin and kanamycin (sub group of aminoglycosides)
- natural and aminopenicillins if due to penicllinase
- ampicillin and amoxicillin
- all beta – lacams if "methicillin-resistant"

Not common or predictable
- aminoglycosides
- beta-lactams in general

2. Pharmacokinetic Considerations

Absorption
Distribution
Elimination

Absorption
- Drug
- Route
- Formulation
  - highly soluble
  - poorly soluble
  - Example – trihydrate & sodium salts of ampicillin
- Tailor to target infection & site

Distribution
- Barriers
- Difficult sites
  - CNS

eye
mammary gland
prostate
testis
intracellular
inflammatory "capsule"

Elimination
Function of primary eliminating mechanism
If slow – accumulation & toxicity
If fast – insufficient concentration

3. Administration of Drug

Route
Dose form
Dose
Regimen

Route
IV
Serious infections
Bolus
Infusion
PO
Usually easy
Most common
Vomiting?
Bioavailability

IM / SC

4. Duration of Treatment

As long as necessary
Norms for certain diseases
Client education
Acute vs chronic

5. Combination of Antimicrobials

Advantages of combinations
Some combinations frequently synergistic: Trimethoprim plus sulfonamide
Enterococcal endocarditis with penicillin and streptomycin
Cryptococcal meningitis with amphotericin B plus flucytosine
Mixed infections
Decrease development of resistant organisms as in treatment of tuberculosis with isoniazid plus pyrazinamide and rifampin

Serious, life-threatening infections of unknown origin or in sepsis or meningitis

Disadvantages of combinations

Interference with action of cidal antibiotic that depends on rapid growth by a static anti that inhibits growth

Increased risk of toxicity to patient

Increase cost

Increased risk of development of resistant organisms in patient or population by use of bacterials not truly needed

6. Problems created by use:

Facilitation of Development of Resistance

- Improper dosage
- Improper interval
- Insufficient duration
- Poor choice of drug
- Use when not needed / prophylaxis

Superinfections

- Importance of commensal organisms
- Broad spectrum
- Too long therapy
- Interference with body defenses

Properties of an ideal anti-bacterial agents:

1. be selective and have effective antimicrobial activity;
2. be bactericidal and not easily induce bacterial resistance;
3. have a satisfactory therapeutic ratio;
4. not act as a sensitizing agents or disturb vital organs or functions;
5. have antibacterial efficacy that is not reduced by body fluids, exudates, plasma protein tissue enzymes;
6. be water soluble and stable at room temperature (especially important in drugs used for therapy);
7. have efficacy via various routes of administration, especially PO;
8. achieve and maintain, with cost-effective doses, cidal levels in blood, tissue, and fluids, e.g. CSF;
9. produce bactericidal concentrations of drug in urinary tract;
10. be neither carcinogenic nor have carcinogenic metabolites;
11. have reasonable cost.

HOST DEFENSE AGAINST INFECTION

Infection and innate immunity

Non adaptive host response to infection

Adaptive immunity to infection

Immunological memory

Innate immunity:

The microorganisms that are encountered daily in the life of normal healthy individuals only occasionally cause perceptible disease. Most are detected and destroyed within hours by defense mechanisms that do not require a prolonged period of induction because they do not relay on the clonal expression of antigen specific lymphocytes. These are the mechanism of INNATE IMMUNITY

INFECTION AND INNATE IMMUNITY:

The infection process can be divided into several distinct phases:
The number, route, mode of transmission, stability of infectious agents determines the infectivity.

1. Infectious diseases are caused by diverse living agents that replicate in their hosts
2. Surface epithelia make up a natural barrier to infection

Mechanical:

Epithelial cells joined by tight junctions
Longitudinal flow of air or fluid across epithelium
Ciliary movements

Chemical:

Fatty acids (skin)
Enzymes: Lysozyme: saliva, sweat, tears, pepsin
Gastric acid

Microbiological:

Normal floras compete for nutrients and attachment to epithelia and can provide antibacterial substances

3. The alternative pathway of complement activation provides a non-adaptive first line of defense against microorganisms. Complement activated by the alternative pathway attack pathogens while sparing host cells, which are protected by complement regulatory protein.

4. Phagocytes provides innate cellular immunity and initiates host defense response.

5. The innate immune response provides inflammatory mediators that recruits new phagocytic cells to local sites of infection

6. TNF Alpha induces blood vessel occlusion and has an important role in localizing local infection but can be fatal when released systematically. TNF alpha induce blood clotting into the local small vessel including them and trigger of blood flow, which prevents organism to enter the blood stream and spread to other organ.

If the infection spread to blood vessel the same alpha TNF becomes catastrophic e.g. systemic release TNF alpha causes vasodilatation, loss of plasma volume owing to increased vascular permeability leading to shock.

7. Neutrophils predominate in the early cellular infiltrate in to the inflammatory site. Neutrophils survive only a few hours after leaving the bone marrow. Neutrophils produce

several bacteriostatic and toxic products e.g. antibacterial substances, Nitric acids, Protease, Phospolipase.

8. Interferons inhibit viral replication and activate certain host defense responses. INF alpha and beta induces resistance to viral replication in all cells. It also increases MHC class I expression and antigen presentation in all cells. It also activates NK cells to kill virus-infected cells.

9. Natural Killer cell (NK cell) Serve as an early defense against retain intracellular infections eg Herpes group of viruses, Leishmania, Listeria monocytogens. NK cells activity is increased 20-1000 folds when NK cells are exposed to TNF alpha Gamma interferon interleukin IL12.

ADAPTIVE IMMUNITY TO INFECTION

When an infection eludes the innate defense mechanisms and generates a threshold dose of antigen...the adaptive immune response initiates.
T cell activation is initiated when re-circulating T cells encounter specific antigen in draining lymphoid tissues.
Cytokines made in the early phase of an infection influences the functional differentiation of the CD4 cells;
CD4 cells stimulated by IL 12 and gamma interferon Differentiates TH1
CD4 cells activated in presence of IL4 and especially IL6 tend to differentiation to TH2 and IL4 and IL10 inhibit the generation TH1.
TH2 cells are the most effective activators of B cells especially in primary response.
TH1 cells are crucial for activating macrophages.

Principles of Antimicrobial Selection and Use: Pharmacokinetic, pharmacodynamic and pharmacogenetic factors

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Excess antibiotic use is worldwide problem. Some studies have been done in Nepal to evaluate the situation of antibiotic use. The result shows the extensive use of antibiotics, though it is difficult to say whether the use is rational or not. Several studies done in United States suggest that about 50% use of antibiotic is inappropriate (i.e., not indicated, wrong drug, wrong dose or duration). The situation in Nepal is far more serious. We should try our best to minimize the misuse of antibiotic.

The clinician has the responsibility of choosing a clinically effective, safe, and cost-effective antibiotic. There are too many antibiotics out of which this selection is to be made. After a careful history and physical and clinical assessment, a series of 10 important questions can and should be routinely addressed before selecting a specific antibiotic.

1. Is an antibiotic indicated on the basis of clinical findings?
2. Once the decision has been made that antibiotics are indicated, have appropriate clinical specimens been obtained, examined and cultured?
3. What organisms are most likely to be causing the infection?
4. If multiple antibiotics are available to treat the likely or known pathogen, which agent is best for a particular patient?
5. Is an antibiotic combination appropriate?
6. Are there special considerations related to host factors?
7. What is the best route of administration?
8. What is the appropriate dose?
9. Will initial therapy need modification after culture data are available?
10. What is the optimal duration of therapy and is the development of resistance during prolonged therapy likely to occur ?

1. Is an antibiotic indicated on the basis of clinical findings?

Obvious bacterial infections require antibiotic therapy. Localized infection like, pneumonia, urinary tract infection, wound infection, or cellulites require therapy. The patient with fever and systemic symptoms but no focal findings is more problematic. Many factors must be considered before one chooses an antibiotic for such patients. The severity of symptoms, patient's age, and underlying illnesses are important considerations. Many of the clinical manifestations that suggest bacterial infection (like fever; chills; localizing symptoms such as pharyngitis, dysuria, and cough) are not diagnostic and may be due to non – infectious causes or nonbacterial agents. Fever may be due to drug, tumor as well as infection. By contrast, some patients may have illnesses caused by viruses with symptoms and signs similar to those of bacterial infections. Antibiotics are ineffective against viruses; therefore, their use will not be beneficial and may be associated with adverse side effects. Unnecessary treatment of viral infections is a major source of excess antibiotic use. Viruses commonly cause upper respiratory tract infections, including

pharyngitis. Influenza is a viral syndrome in which antibiotics play no role unless there is bacterial super-infection. The healthy with mild illness and no focal finding does no require treatment until a firm diagnosis has been reached. Furthermore, unnecessary antibiotic may suppress follow-up cultures for several days.

In contrast, a patient with presumed infection who is severely ill, with or without focal findings, needs immediate therapy. Since the cultures may require 24-48 hours to become positive, the patient should be treated presumptively. Once the cultures have revealed the offending pathogen, the therapeutic regimen can be altered to be more specific. In fact, initiation of antibiotic therapy is carried out most commonly on the basis of clinical judgment. The laboratory results help one refine and adjust therapy.

2. **Once the decision has been made that antibiotics are indicated, have appropriate clinical specimens been obtained, examined and cultured?**

This is extremely important. Even in the most urgent situations, blood and routine cultures must be obtained prior to initiation of antibiotics. Usually there is also time to examine Gram stains of any exudates or bodily fluid. This may help one to recognize the major organism or organisms and thus include in the therapy an antibiotic that otherwise might not have been used. Since antibiotics alter surface bacterial flora (e.g., sputum or wound swabs) quickly after their initiation, subsequent cultures usually do not reflect the initial causative organisms. Therefore follow-up cultures are much less reliable than pretreatment cultures.

3. **What organisms are most likely to be causing the infection?**

This is an easy question to answer if the culture data identify the pathogen, but often the clinicians must start antibiotics empirically. It is desirable to make an educated guess about the likely pathogens in order to select an antibiotic with good activity against the most likely pathogens. Focal findings will strongly influence the decision about whether coverage will be directed against gram positive, gram negative, or anaerobic organisms.

The age of the patient at times may provide important additional clues to the likely organisms or may affect the choice of agent. For example, in meningitis, neonates are usually infected with group B streptococci or enteric organisms. In children younger than 2 years of age, *Haemophilus influenzae* is common but *S. Pheumoniae* and *Neisseria meningitides* also occur. The latter two organisms are the most common pathogens in adults.

The choice and dosage of an antibiotic are also affected by age. For example, tetracycline should be avoided in children younger than 8 years because of its affect on teeth. The fluoroquinolones should be avoided in children and teenagers because they may affect cartilage and bone formation. Hospital acquired infections are often caused by gram negative bacteria that are resistant to penicillin, ampicillin, erythromycin, and other antibiotics commonly used in the outpatient setting. Prior antibiotic use in a given patient may predispose to infections with more resistant organisms.

4. **If multiple antibiotics are available to treat the likely or known pathogen, which agent is best for a particular patient?**

If there is an obvious drug of choice, it is to be decided if this can be used. Prior antibiotic allergies may preclude the use of some agents. For example, if the patient is allergic to penicillin, the patient must be presumed to be allergic to the penicillin derivatives unless appropriate skin tests can be done to test specifically for cross-reactivity. It is also to be considered if the antibiotic under consideration penetrates the effected area. This may be particularly important in infections involving the CNS, into which aminoglycosides, and first-and some second – generation cephalosporins penetrate poorly. Two other sites of poor penetration are the prostate and the obstructed biliary tree. The pH of the site of infection may affect antibiotic activity; for example, aminoglycosides are much more effective in a physiologic medium (pH 7.4) than in an acid environment (e.g. abscess). Because of some potential side effects some agents may be contraindicated in certain settings. Examples include limited use of chloramphenicol due to the rare occurrence of aplasia (One in 25,000 – 50,000 courses of therapy).

Choice of bactericidal versus bacteriostatic agent is another point to be considered. Bacteriostatic agent primarily inhibit bacterial growth. Killing of the organism depends on host defense mechanisms. One of the disadvantages of bacteriostatic agent is that, in the setting of inadequate host mechanism, any partially inhibited organisms may survive, replicate, and produce recurrent disease when the antibiotic is discontinued. Bactericidal agents depend less on host factors. Bactericidal agents are preferable if the host is compromised (e.g. immunosuppressed patients) or when host defense mechanism do not operate well. In minor infections of the healthy host, bacteriostatic or bactericidal agents are probably or equal efficacy. However, in severe life threatening infection, bactericidal agents are necessary.

The cost of the therapy is another points to be considered. When considering the price, cost of total therapy should be considered and not the cost of one capsule or tablet. The use of multiple antibiotics often increases costs. In some situations, instead of using triple antibiotics for intra-abdominal sepsis (e.g. penicillin, gentamicin, clindamicin or metranidazole), it may be appropriate and cost-effective to use an expensive single agent like ampicillin-salbactam.

Intravenous versus intramuscular versus oral administration: because of less nursing time and material required, intramuscular administration is less expensive, and oral therapy is even less expensive. The oral fluoroquinolones are very exciting agents that are often cost-effective if they are used appropriately instead of a parenteral agent.

For empiric therapy, antibiotics with a broad spectrum of activity are used. Once susceptibility data are known, it is preferable to use a narrow-spectrum agent if possible

5. **Is an antibiotic combination appropriate?**

Although in-vitro and animal studies support the use of antibiotic combinations, documentation of increased efficacy for human infections is difficult to obtain. In infections in which multiple organisms are likely or proved, more than one antibiotic are used for synergies. When one antibiotic greatly enhances the activity of another, with more than a merely additive effect, this interaction is called synergy. This action may be by serial inhibition of microbial growth (e.g.

fixed combination of trimethoprim and sulphamethoxazole will block successive steps in synthesis of folic acid), or one antibiotic enhances the penetration of another (e.g. enterococci are impermeable to aminoglycosides. Addition of penicillin alters the cell wall, allowing the aminoglycosides to penetrate the bacteria and thereby act effectively at the ribosomal level.

There is some disadvantage of multiple antibiotics. There is an increased risk of drug sensitivities or toxicity, higher cost and false sense of security. Another important point is the possibility of antagonism. The example is the use of tetracycline and penicillin. It was observed that addition of tetracycline and penicillin for the treatment of meningitis resulted in poorer outcome than when penicillin was used alone, presumably due to inhibition of growth by tetracycline, which interferes with the bactericidal action of penicillin.

6. Are there special considerations related to host factors?

There may be special characteristics of the host that must be considered in choosing an antibiotic for use in individual patient. Patients with glucose-6 phosphate-dehydrogenase deficiency may develop haemolysis from sulphonamides and nitrofurantion. Certain drugs may pose special problems during lactation and pregnancy.

7. What is the best route of administration?

Parenteral antibiotics are almost always used in serious infections to ensure adequate blood levels. Oral absorption of antibiotics, in general, is often too unpredictable to trust in serious infections. Well-absorbed oral agents may be used to complete a full course of therapy in uncomplicated infections.

8. What is the appropriate dose?

To reduce the risk of side effects, the potential of super-infection, and the cost of therapy, generally the lower dose of antibiotics that will be efficacious is used.

9. Will initial therapy need modification after culture data are available?

Once the results of cultures and antibiotics susceptibility data are available, the antibiotics regimen should be modified when possible.

10. What is the optimal duration of therapy and is the development of resistance during prolonged therapy likely to occur?

The optimal duration of antibiotic therapy may be well established or relatively empiric. This must be individualized. Bacteria have several mechanisms of acquired antimicrobial resistance, including a change in the drug target, the production of detoxifying enzyme, or decreased antibiotic uptake. What has become increasingly clear is that using a broader spectrum antibiotic than is necessary appears to be associated with an increased likelihood of the development of multi-resistant bacteria. Therefore it is particularly important for the clinician to use the new brad-spectrum agents carefully to help minimize the development of bacterial resistance. This usually involves some type of hospital-wide antibiotic control program and rational use of antibiotics. Cautious conservation is advocated in the use of new antimicrobial agents.

Pharmacokinetic, pharmacodynamic and pharmacogenetic factors

Successful therapy depends

- On achieving antibacterial activity at the site of the infection
- Without significant toxicity to the host

Location of the infection may dictate

- Choice of drug
- Route of administration

The minimal drug concentration achieved at the infected should be atleast equal to the MIC for infecting organism.

Access of antibiotics to sites of infection depends on multiple factors

- If the infection is in CSF, the drug must pass the blood brain barrier and many antimicrobial agents that are polar at the physiological pH to do so poorly. For example, concentrations of penicillins and cephalosporins in the CSF are usually only 1-5% of steady-state concentration in plasma.
- In infection, access to CSF is increased even for polar drugs as the integrity of the BBB is diminished: tight junctions in cerebral capillaries open leading to a marked increased in the penetration of polar drugs. As the infection is eradicated and the inflammatory reactions subside, penetration reverts towards normal.
- Penetration of drugs into the infected loci always depends on passive diffusion. The rate of penetration is thus proportional to the concentration of free drugs in the plasma or extracellular fluid. Drugs that are extensively bound to protein thus do not penetrate to the same extent, as do congeners that are bound to a lesser extent.

Status of the individual patient's mechanisms for elimination of drugs is essential prior prescribing.

- Most antimcrobial agents and their metabolites are eliminated primarily by the kidneys. It is important to be careful while prescribing aminoglycosides, polymyxins, vancomycin and flucytosine in patients with impaired renal functions since these drugs are completely eliminated by renal mechanisms and their toxicity appears to correlate with their concentrations in plasma and tissue.
- Drugs that are metabolized or excreted by the liver (erythromycin, chloramphenicol, metronidazole, clindamycin) dosage must be reduced in patients with hepatic failure. Rifampin and isoniazide also have prolonged half-lives in patients with cirrhosis.

Age

- The age of the patients is an important determinant of pharmacokinetic properties of antimicrobial agents. The mechanism of elimination especially renal excretion and hepatic biotransformation are poorly developed in the newborn; this is particularly true for premature infant. Failure to adjust dose may have disastrous consequences such as gray baby syndromes.
- Elderly patients may also have significantly reduced rates of creatinine clearance and slower rates of drug metabolism. Elderly patients are particularly susceptible to the ototoxic effects of aminoglycosides.
- Developmental factors may also determine type of untoward response to a drug e.g. tetracycline binding to developing teeth and bones, kernicterus following the use of sulphonamides in newborn infants.
- Achlorhydria in young children and in the elderly may alter absorption of orally administered antimicrobial agents (increased absorption of penicillin G, decreased absorption of ketoconazole)

Pregnancy

- Pregnancy imposes an increased risk of reactions to some antimicobials for both mother and fetus e. g. hearing loss in the child has been associated with administration of streptomycin to the mother during pregnancy. Tetracyclines can also be particularly toxic to the pregnant female. Pregnant women receiving these drugs may develop fetal acute fatty necrosis of the liver, pancreatitis, and associated renal damage.
- Plasma concentration of ampicillin is lower in pregnant woman.
- The lactating mother can pass anti-microbials to her nursing child. Nalidixic acid and sulphonamides in the breast milk have been associated with hemolysis in children with G6PD deficiency.

Genetic Factors

Certain genetic or metabolic abnormalities must be considered when prescribing antibiotics. A number of drugs including the sulphonamides, nitrofurantoin and chloramphenicol may produce acute hemolysis in patients with G6PD deficiency. Patients who acetylate isoniazide rapidly may have sub-optimal concentrations of the drug in plasma and an increased risk of hepatotoxicity.

Science of AMR- definition, resistance mechanism, transfer of resistance (cross resistance), and value of microbiological diagnosis

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Consultant Pathologist

HISTORY

- Mouldy curd on boils – Chinese.
- Chaulmoorg oil on leprosy – Hindus.
- Cinchona bark on fever – 17th century.
- Use of ogranometalic compound.
- Use of Sulfonamide
- Discovery of Penicillin.
- Synthetic anti-microbial agents.

Antibacterial gents:

- Kill bacteria/inhibit growth
- Natural, Synthetic, Semi-synthetic.

Antibiotics:

- Compounds produced by living organisms.

Goal:

- Minimal toxicity to the host
- Maximum therapeutic effect on invading organism.

Action target:

- Cell wall, Protein synthesis, Cell metabolism, DNA synthesis, Cell membrane.

Sensitivity:

- Completely sensitive to antibiotic.
- Intermediate sensitivity either sensitive to higher doses or more toxic antibiotic.
- Resistant – Non-sensitive even to higher doses or toxic more toxic antibiotics.

Mechanism of action:

- Inhibit cell wall synthesis – e.g. Pencillin.
- Leakage from cell membrane- e.g. Amphotericin.
- Inhibit protein synthesis – e.g. Chloroamphenicol.
- Interfere with DNA function – e.g. Norfloxcin.
- Interfere with DNA synthesis – e.g. Zidovudine.
- Interfere with intermediary metabolism e.g. – Sulfonamide.

- Misreading of m –RNA code (Bind to 30S ribosome) – e.g. Streptomycin.

Types of action:

- Bacteriostatic e.g. Tetracycline.
- Bactericidal e.g. Penicillin.

Source of antibiotic:

- Bacteria e.g. Polymyxin B
- Fungi e.g. Penicilline
- Actiomycetes e.g. Chloroamphenicol.

Anti-microbial resistance:

- Natural resistance: Due to lack of target site or metabolic process eg. Gram negative bacilli to Penicillin.
- Acquired resistance: Normally sensitive bacteria to antibiotic can acquire resistance by mutation of resident genes, or acquisition of new genes.

Three common mechanisms:

1. Production of drug inactivating enzyme, B lactamase and aminoglycoside,
2. Alteration of target site-change in amino acid pattern in bacterial enzyme.
3. Prevent access of the drug to target site.

Mutation:

- Stable & heritable genetic changes occur randomly among microorganism. Mutant gene may require higher concentration of the drug.
- Single gene mutation mean high degree of resistance e.g. E. Coli & Staphylococci to Refampin.
- More than one gene mutations mean slow development of resistance –e.g. Erythromycin, Chloroamphenicol.

Gene transfer:

- Conjugation : Formation of bridge (Sex pilus) e.g. In gram-negative bacilli with help of plasmid.
- R factor → R Transfer factor → to another organism.
- Transduction: → R factor → Bacteriophage → to another organism.
- Transformation → Release Resistance carrying DNA → imbibed by another organism.

Cross Resistance:

- Resistance to one AMA → Resistance to another AMA not exposed earlier.
- Common among chemically or action wise related AMA e.g. Sulfonamides, Tetracycline.

- It may be complete/partial cross-resistance.

Prevention:

- Avoid indiscriminate, inadequate or prolonged use.
- Use rapidly acting & Selective AMA.
- Combination therapy for prolonged use.

Epidemiology of Infectious Diseases: Disease Prevalence

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Routes of Infection:

I. Through Mucosal Surface: Microbes survive due to moist and warm environment and won't survive when gets dried up. Through avenues of
i) Respiratory tract: Droplet
ii) Alimentary: Diarrhea etc.
iii)Urogenital: STD e.g. N. gonorrhea, T. Pallidum, HIV, HBV.

II. Skin:

i) Usually through a) Cuts e.g. Tetanus, infection of burn wounds.
b) Bites of anthropod vectars e.g.Plasmodium
ii) Without cuts e.g. Schistosomiasis.

Danger infection:

Nosocomial (hospital acquired) Infection : Many i) UTI ii) Respiratory tract Infections - Pseudomonas, Legionellosis iii) Subcutaneous tissue iv)others: Grafts, inplants, prosthetic valves etc.
Host tissues fight back when foreign antigens/ microbes etc are introduced. Immune systems come into play and its function can be evaluated by:
i) Complement – its activities leads to bacteriolysis
ii) Phagoytosis by macrophages of reticuloendothetial cells
iii) B cell- Humoral immunity
iv) T-cell – Cell mediated immunity
v) Natural killer lymophocytes- requiring no antigenic and antibody stimulation.

Immune function of T and B lymphocytes:
Pool of effector T-cell is established in thymus early in life.
T-cell are primary effector cells of cell mediated immunity with Subsets producing:
i) CD8+ (Surface antigen or leucocyte, cytotoxic cells which can lyse virus infected or foreign cells)
ii) CD 4 helper cells:
CD4 + T cells are primary regulatory cells of T&B lymphocytes
CD4 - T cells are involved in:
a) CD4 + Helper cells
b) MHC (Major Histo-compatibility Complex) class II restricted cytototoxic(killer cell
c) Inflammation characteristic of delayed hyper sensitivity.

After presenting to MHC class I or II only, T-cells recognize to act on antigen- peptide fragment CD8 + T cells are destined to become MHC class I restricted cytotoxic cells. Activated T cel

provide cytokins which involved in regulation of growth, develop & activation of immune system and also in maintaining of inflammatory response. CD helper cells are of two sub types:

i) Type 1 helper cells(TH1)- produce a) INF-8 b) IL-2 c) TNF-alpha
ii) Type 2 helper cells (TH2) secretes interleukins: 3,4,5,6,10.

Helps B cells to form antibody by allowing to mature, proliferate, differentiate and ultimately antibody formation through IL-3,4,5&6 i.e. primary role in regulation of humoral immunity mediated through B-lymphocyte.

TH2 through IL-4 and 10 limits pro inflammatory response mediated by TH1,

Antibodies: Immunoglobulins which combat infections: IgM produced initially-disappearing after several months
Ig G follows in
Ig A-secreted on mucosal surface e.g. GIT
IgE

Examples

Defect in i) cellular immunity – viral, myobacterial, fungal infection; HIV infections
vi) antibody deficiency: reccur bacterial infections, S. Pneumonia, haemophilus infection
vii) Phagocytic defect: recur infection of skin by staph. aureus
viii) Defect in early and late complement factors: auto immune phenomena, Neisseria infection

Infection causing inflammation produces active phase reactants or proteins;
i) C_1 and C_2 complement products
ii) C – reactive protein
iii) Haptoglobulin
iv) Anti- trypsin

Clinically it presents by SIRS (systemic inflammatory response Syndrome)
SEPSIS = SIRS + documented evidence of infection
SIRS with infection may be present in: i) major trauma ii) burn iii) ischaemia iv) parcreatitis

SIRS: two or more of the following
i) Temp $>38^{oC}$ or $<36^{oC}$
ii) Respiratory Rate > 20 or $P_aCo_2 < 4.3kPa$ (<32.25 mm of Hg)
iii) Heart rate > 90
iv) WBC > 12000 mm^3 or < 4000 mm^3

Epidemiology of few diseases: Natural way or Biological warfare eg. Anthrax Spores

I. DIARRHOEA

Acute < 2/52:>200gm; persistent 2-4/52 ; chronic >4/52
- Under 5 years; up to 22% mortality in developing countries

- Till recently 25% in Nepal, now reduced from 2.01 to 0.07 per 1000
- It decreased from 172 per 1000 in 2055/56 (1998/9) to 164/1000 in 2056/57 (1999-2000)

: 2% Kathmandu valley population suffers from diarrheal disease episode requiring hospitalization occurring in 15-25 years mostly 91.5% - 1992 report.

: Starts from April, peaks in July – August declines in September.

: 1992 report; 25% stool examined – showed cholera – water being the commonest source of infection. Present status unknown.

Relevant facts about acute diarrhea

> 90 of one to infection: fever, abdominal pain, vomiting,

i. Traveler's diarrhea: a) Latin America, Africa and Asia: E.coli, Shigella, Salmonella, Compylobadir.

b) Russia: Giardia, c) Nepal: Giardia, Cyclospora

ii. Food poisoning: Contaminated chicken, fried rice, hamburger, e.g. E. coli, B. aureus Salmonella, Staphylococcus,

iii. Toxin, cytotoxin producing and invasive respectively a) cholera, E. coli, Staph. aureus b) clostridium difficale c) E. histolytica and Yersenia

iv. Immuno – deficient: Primary, secondary e.g. HIV infection

a) mycobacteria
b) Virus ; cytomegalic, herpes simplex
c) Protozoa ; cryptosporidium, Isospora

v. May be manifestation of

a) Vital hepatitis
b) Listerosis
c) Legionellosis
d) Toxic shock syndrome.

Stool exam: ova/cyst, faecal/leukocytes or increased faecal larvae of leukocyte proteins: E. histolytica etc, culture, molecular biology: DNA sequence.

II. TB

45% of population infected. Every year, 44000 develop active TB infection of whom 20,000 develop active pulmonary TB.

: National TB. Program: only 30% TB cases got registered and out of this, only 40% treated successfully

: Since DOT in introduced, cure rate to 89%; now extended to 66 districts hoping to cross 75% of population.

: In Nepal its association with HIV not yet exactly known.

III. Leprosy: Control activities started in 1996. In 1966, 100,000 estimated to be present

Prevalence rate 2056/57: 3.88/10,000
Detection rate 3.18 in 1999/2000 or against 8.7 in 1998/99

IV. Enteric fever: attack rate 523/100,000 ; 1% KTM in 1979/80

V. Meningitis

TB: Commonest
1990 report: 66% under 5 years detected TB with a mortality rate of 26%
Meningococcil: Epidemic 1982 – 84: 1475 cases with peak in April controlled with vaccination in 1984
: Still sporadic case

VI. JE : aflavi virus
: 1st reported in 1978
: Since then, 500-700 case per year reported ie case rate 2-7/100,000
: 60% under 15 year, highest in 5-14 years
: Highest in Mid-west and lowest in central region
: Occurs from June, peaks : Sept – Oct
: Case fatality rate 18.1% in 1992
: In the year 2000, 1729 case and 169 deaths

Case fatality rate 9.77%
: 12,000, vaccination in 1-15 years amongst 221,000 children: conducive

VII. Malaria : Disease on the from 3.7 to 5.8
: Problem of chloroquine resistant malaria
Any high fever with rigor, think of malaria – that too chloroquine resistant.

VIII. Hepatitis
Hep. E – commonest acute infection with epidemic in 1973, 1981/82 1997

HBV: carrier rate 2 – 6.3%
" " in pregnancy 0.5 to 0.7%
" " 2% among blood donor
" " 5% among drug abuser - also positive simultaneously for HCV in 75%
HCV: 3.82% among blood donors
Estimate of chronic liver disease or a result of above not known

IX. HIV
- 1st reported in 1988
- 17.351% among blood donors
- Highest in 14 – 39 years, being most in 20 – 29 years amongst 1616 cases reports in 2056/57 (1999/2000), of whom 370 developed AIDS

X. Rabies
27 (0.4%) hydrophobia i.e. disease out of 17321 animal bits

Regulatory Measures for Antibiotics use

Radha Raman Prasad
Senior Drug Administrator, DDA

Antibiotic is an important drug for healthcare. However there is no special act, rules or regulation in Nepal especially on antibiotics. Being drug, it is regulated by existing Drug Act in similar manner as other drugs. National Drug Policy also does not mention antibiotic as a separate category. But due to poor sanitation and lack of education, the most prevailing disease is infection. So antibiotic is vary important drug regulated under Drug Act. Due to improper use of antibiotics and ever-increasing antimicrobial resistance problem now it is high time to have special rules and regulations on antibiotics.

Drug Act

Drug Act was enacted in 1978 to provide for the regulation of drugs, to prohibit the misuse or abuse of drugs and allied pharmaceutical materials as well as the false or misleading information relating to efficacy and use of drugs and to regulate and control the production, marketing distribution, export-import, storage and utilization of those drugs which are not safe for the use of the people, efficacious or of standard quality.

Department of Drug Administration (DDA) was established in 1979 as per Drug Act for its implementation. Royal Drug Research Laboratory, the National Drug Control Lab is the principle organization for analysis.

To prevent misuse and abuse of drugs, they have been classification into three categories according to their constituents, efficacy and use as per the provision of Section 17 of the Drug Act. These three categories are:

Group 'Ka' – Narcotics, psychotropics and potent therapeutic agents.
Group 'Kha' – Antibiotics, hormones and general therapeutic agents.
Group 'Ga' – Other common drugs which are safer.
Drugs in group 'Ka' and 'Kha' are prescriptive drugs while those in group 'Ga' are over the-counter ones.

According to Drug Act, drugs categorized in category 'Ka' and 'Kha' are to be prescribed only by practitioners registered in Nepal Medical Council.

A pharmacist or recognized drug seller with qualification/ training as prescribed by drug Advisory Committee and recognized by it, is only authorized for sale and distribution of drugs, both prescription and OTC drugs.

National List of Essential Drugs, Nepal (1997) has categorized anti-infective drugs for the different levels of health care to promote rational use of antibiotics. Amoxycillin. Suphamethoxazole + Trimothoprin: and Tetracycline are included in sub health post level. Amoxycillin, procaine benzyl penicillin, Chloramphenicol, Sulphamethoxazole + Trimethoprim, Tetracycline, Doxycycline and Ciprofloxaxin. National list includes all the drugs of district level plus Cefotaxime.

In real situation the antibiotics are recommended to the patients by the health workers in different level of health care. Antibiotics registered with Department of Drug Administration (DDA) are available in the private sector retail shops. A new molecule, including antibiotics, is not registered in Nepal until it is included in recognized pharmacopoeia as per convention adopted by Drug Advisory Committee considering price, as well as extensive studies on safety and efficacy profiles.

There are Drug and Therapeutics Committee/Formulary Committee in some of the central level hospitals.

Department of Drug Administration has published Nepalese National Formulary (1997) having information on drugs including antibiotics and its formulations,

Standard Treatment Schedules 1999 for health posts and sub health posts has been published with the aim of rational prescribing. Drugs recommended in the treatment schedules are based on the list of essential drugs prescribed for HP/SHP.

Restriction on use

Combination of more than one antibiotic or with other drugs is not permitted except drugs of penicillin group, anti-tubercular drugs and combination accepted by the recognized pharmacopoeia.

The following antibiotic medicines have been banned for human use at different times.

Combination of Penicillin with Sulphonamide; combination of Vitamin C with tetracycline; combination of chloramphemicol except in combination with Streptomycin; Sulphaguanidine and its combination; Tetracycline in combination with Streptomycin; Sulphaguanidine and its combination; Tetracycline liquid oral preparations; combination product containing active ingredients of two or more systems of medicines (e.g. Ayurvedic, Allopathic, Unani and Homeopathic); combination of two or more antibacterial except combination used for the treatment of tuberculosis, combination used for the treatment of leprosy, combination of two antibiotic of the penicillin group; combination of two or more therapeutic agents as recognized by approved pharmacopoeias.

Drug Act amendment

The amendment of Drug Act has been done keeping in view to overcome present problems like classification of drugs as per health care delivery system separating the areas of dominance on prescribing for registered medical practitioner and para-medical health workers appropriates as well as measures for sale of drugs without prescription.

National Drug Policy

In accordance with the objectives of the National Health Policy, to fulfil the commitment of HMG of Nepal, to provide health for all and to improve and manage by establishing coordination among governmental, non-governmental and private organizations involved in the activities

related to drug production, import, export, storage, supply, sales, distribution, quality assessment, regulatory control, rational use and information flow, the National Drug Policy 1995 has been promulgated for implementation.

The main policy of National Drug Policy is to maintain, safeguard and promote the health of people by making the country self-reliant in drug production; ensuring the availability of safe, effective, standard and quality drugs at affordable price and to manage effectively all the drug related activities.

National Drug Policy 1995 (First Amendment 2001)

His Majesty's Government of Nepal has decided to amend clause 4 of the National Drug Policy (NDP) 1995, and added Prudent Use of Antibiotic as one of its major activity in sub clause 4.3.3 after 4.3.2. The following strategy has been taken under the prudent use of antibiotic program.

1.3.3. **Prudent Use of Antibiotics:**

a) Prevailing antibiotics use in food products, animal feeds and agriculture substances will be managed properly.

b) Supervision and monitoring on use of antibiotics will be carried out. Misuse will be controlled and proper recording systems will be developed.

c) Antibiotics will be classified into different groups for prescribing purposes by medical doctors, veterinary doctors and other health personnel.

d) HMG will constitute a National Antibiotic Control Committee comprising of experts from human and animal health, agriculture and representation from professional organizations / councils and organizations involved in consumers right and other sector for prudent use of antibiotics.

e) HMG will constitute a National Antibiotics Therapeutics Advisory Committee (NATAC) comprising of experts from relevant sectors to advice on prudent use of antibiotics.

Issues to be addressed for Legal Aspect of Antibiotics

1. Authorization for prescribing: as large number of paramedical personnel are providing health service in the country. There is no post of medical doctors below PHC level of government health facilities. Since Nepal Nursing Council and Nepal Health Professionals Council is already established, the health professional should be allowed to prescribe particular antibiotics as per their level of education.

2. Reserve list of antibiotics: newer and particular antibiotics should be kept in reserve list to combat any emergency and resistance situation.

3. Special care for manufacturing antibiotics: manufacturing of antibiotics should be done in such manner that there is no chance of contamination of antibiotics with other drugs.

4. Antibiotics use in veterinary practice: at present the use of antibiotics in veterinary practice is regulated by Drug Act. But the antibiotics used in animal feed as growth promoter or as a prophylactic agent is not regulated. So there should be some regulation in this area.

5. Sale of partial course of antibiotics: there should be restriction on sale of partial course of antibiotics. However due to financial reason if it is not possible to dispense complete course, the prescription should be clearly marked 'how much of drug was dispensed'.

Antimicrobial Drug Combinations

Dr. Kumud K. Kafle
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Infection Control Practices

1. Infection can be transmitted through

   a. Patient to patient
   b. Hospital personnel to patients or vice – versa
   c. Non-sterile injection
   d. Surgical equipment

2. Infection rates can be decreased by

   a. Improved hand washing
   b. Use of gloves and gowns

3. Simple infection control practices are:

   a. Hand washing
   b. Changing gloves before and after contact

4. Poor infection control practices results into

   a. Increased dissemination of resistant bacterial strain

General Guidelines to Use of Antibiotics

- *Start* antibiotics if there is evidence of infection
- In starting antibiotics it is better *not* to use any of the new ones, if you are not familiar with their use.
- Antibiotics *should not* be started in response to patients' pressure
- Do not prescribe antibiotics for viral infections like common cold or diarrhea to satisfy the patients
- Antibiotics when used should be given for sufficiently long period. Inadequate duration and dose of therapy should be discouraged.
- *Do not change* an antibiotic before giving the current antibiotic a fair trial.
- Single dose antibiotics therapy for fever without localizing signs *should not* be given.
- Cost effectiveness of therapy should be considered especially while changing antibiotics, calculating for the full duration of treatment.
- Where ever possible culture sensitivity of appropriate samples should be sent *before* the antibiotic treatment is started.
- It is to your advantage to be in contact with a reliable microbiology laboratory for antibiograms of commonly used antibiotics. It is rational to have an educated guess of first choice before the antibiogram becomes available.
- *Avoid* using too many antibicrobials and drug combinations as it encourages sloppy diagnosis and mismanagement.
- *Avoid* use of multiple antibiotics, except where indicated as in the treatment of tuberculosis or leprosy.

- Acquire adequate unbiased knowledge about a limited number of antibiotics of proven efficacy and be familiar with their side effects.
- Get a full drug history and history of allergy to the chosen antibiotics, before starting the antibiotics.
- Where possible and indicated, e.g. poor response to therapy, repeat culture and sensitivity.

Antimicrobial resistance is today challenging our ability to treat effectively at least four of these infections: acute respiratory infections, diarrheal disease, malaria and TB.

What is antimicrobial resistance?

When antimicrobial resistance occurs, it is the microbe (bacterium, virus, fungus or protozoan) that is resistant; not the drug, nor the patient. Resistance can develop either through mutation (vertical transmission) or through acquisition from other bacteria of resistance genes (horizontal transmission). This dual means of acquiring resistance explains why the resistance trait can spread rapidly and replace a previously drug-susceptible population of bacterial.

Inappropriate prescribing practices – including the wrong choice of drug and incorrect dosage or length of treatment-poor compliance with treatment, and the use of low quality (sometimes counterfeit) drugs all contribute to the emergence of drug-resistant microbes.

Why is antimicrobial resistance spreading so fast?

Although mutations are rare events (about one in a million bacteria may show a mutation which might lead to resistance), microbes multiply very rapidly – thereby enabling a single mutant to rapidly become dominant. Microbes also spread readily from person to person, not only of the infection, but of a resistant infection.

Thus in taking action to contain resistance, both the *emergence of resistance* and *spread of resistant* strains need to be considered.

Can antimicrobial resistance be halted?

Since it is antimicrobial use that drives resistance, the focus of any containment strategy should be on minimizing any unnecessary, inappropriate or irrational use of antimicrobial drugs.

Resistance can be Effectively Treated

<u>Ideal drug usage involves</u>

- The correct drug
- Administered by the best route
- In the right amount
- At optimum intervals
- For the appropriate period
- After an accurate diagnosis

Problems occur in both developed and developing countries when antimicrobials are

- Not equitably available
- Used by too many people
- To treat the wrong disease
- In the wrong dosage
- For the wrong period of time
- Not in the correct formulation or strength

Antimicrobial resistance is not a new or surprising phenomenon. All micro-organisms have the ability to evolve various way of protecting themselves from attack but over the last decade or so:

- Antimicrobials resistance has increased
- The pace of development for new and replacement antimicrobials has decreased

Resistance means that

- People can't be effectively treated
- People are ill for longer
- People are at greater risk of dying
- Epidemics are prolonged
- Others are at greater risk of infection

Antimicrobial Drug Combinations

When more than one antimicrobial agent is to be used, due consideration should be given to the mode of action of the antimicrobial agents. Combined use of two antimicrobials may lead to enhancement of action (synergism), inhibition of action (antagonism) or no change in antimicrobial activity (indifference or additive effect).

Synergism

The simultaneous use of two drugs (X and Y) results in an effect much greater than that of either X alone or Y alone in much larger doses and greater than what could be expected from simple addition of individual antimicrobial agents.

a. Sequential blocking of successive steps in metabolic processes
   e.g. sulphonamide and trimethoprim

b. Inhibition of enzyme that may destroy second antibiotic

   Staphylococci and other organisms that produce beta lactamase are resistant to the action of penicillin G, because the antibiotic is hydrolyzed by the enzyme. However, if the enzyme is inhibited by clavulanic acid (e.g. amoxycillin with clavulanic acid)

c. Promoting the entry of second drug

Many streptococci exhibit partial permeability barrier to aminoglycosides. If a cell wall inhibitory drug is administered simultaneously, it will enhance the penetration of the aminoglycoside, which will thus act on ribosome and accelerate the killing of the cell.

Combined therapy permits cure of sepsis or endocarditis caused by organism like Strep. Viridans, Gr. B. Streptococci and group D. Enterococci.

The principle of antibiotic synergism has been applied in the treatment of bacterial endocarditis, which can be cured only if the infecting organisms are eradicated by bactericidal drug. Endocarditis caused by enterococci is usually not cured by penicillin alone (as penicillin is only bacteriostatic for enterococci). However, when aminoglycoside is combined with penicillin, this combination is strikingly bactericidal for many strains of enterococci. Usually penicillin or ampicillin with an aminoglycoside is used for synergism. Similarly synergic antibiotic combination is recommended in treatment of pseudomonas infections in neutropenic patients. Combination of carbenicillin with gentamicin markedly increases the cure rate.

Synergistic combination therapy has also been used successfully in fungal infections especially in cryptococcal meningitits where flucytosine and low dose of amphotericin B for six weeks, is found to be as effective as therapy with a higher dose of amphotericin B for ten weeks, with less renal toxicity.

Antagonism

Combining two antimicrobial agents with different sits of action may result in inhibition of the antibacterial effectiveness of one of the drugs. Antagonism of antibacterial effect may also result when bacteriostatic and bactericidal agents are given together. The addition of a bacteriostatic to bactericidal drug frequently results in only a bacteriostatic effect.

Indications for the Use of Antimicrobial Combinations in Clinical Practice

1. Mixed bacterial infections

When the infection is caused by two or more microorganisms e.g. intraabdominal and genital tract infections, hepatic and brain abscesses.

2. Fatal (severe) infections where a specific etiology is not known

Selection of the antimicrobial combinations is based on judgement of the various infectious diseases, their microbiology and antibiotic spectrum of available antimicrobials. This approach should be reserved for severely ill patients and should not be used as a short cut.

Adequate cultures prior to the initiation of therapy should be obtained and discontinue combination chemotherapy after the organism have been identified and the sensitivity determined.

3. Enhancement of antibacterial activity

When two antimicrobial agents are given together, they may produce a synergistic effect and may permit

a. a reduction in the dosage of one or both antimicrobial agents with the achievement of similar antimicrobial effect.
b. The combination may produce a more rapid or complete bactericidal effect than could be obtained with either antimicrobial alone. In enterococcal endocarditis, combination of penicillin with streptomycin or gentamicin is bactericidal.

   In pseudomonas infections in neutropenic patients, synergistic antibiotic combination is recommended. An antipseudomonal penicillin plus an aminoglycoside are synergistic against most strains of pseudmonas aeruginosa.

   Use of an inhibitor of B – lactamase which has no intrinsic antimicrobial activity (calvulanic acid) with a B – lactam antibiotic (amoxicillin) that are susceptible of B – lactamase is a new concept. In this way, usefulness of well tried antibiotic (piperacillin, ampicillin and amoxycillin) may be restored in infections in which they have become ineffective.

4. Prevention of emergence of resistant mutants

   Method has received extensive use in the treatment of tuberculosis where concomitant use of two or more appropriate agents significantly reduces the development of drug resistance by the mycobacterium.

Disadvantages of Antimicrobial Combination Therapy

The most obvious disadvantages of concomitant use of two or more antimicrobial agents are

- risk of toxicity from two or more agents
- selection of bacteria that are resistant to antibiotics that may not have been necessary
- increased cost to the patient
- antagonism of antibacterial effect.

The administration of a bacteriostatic agent, while bactericidal drug is already being administered, frequently results only in a bacteriostatic effect. Where the host defenses are still adequate the balance may still be in favor of host. However, where the host defense is impaired as in patients with neutropenia or in special situations like endocarditis or meningitis, the bactericidal effect is more important.

Use of antimicrobials in children

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Children in Nepal:

Demographic features:

Population under 15 years of age: 43%
Population under 5 years of age: 16%
Population under 1 year of age: 4%

Morbidity pattern:

Admission pattern in children wards:
More than 60% of the admitted children are under five years of age and more than 60% of these under one year of age.

Common childhood problems:

- Acute respiratory infections
- Pneumonias
- Otitis media
- Diarrhea
- Dysentery: bacillary and amoebic
- Typhoid fever
- Meningitis
- Malaria
- Kalazar
- Skin infections: pyoderma, cellulitis, abscesses, neonatal skin infections: staphylococcal scalded skin syndrome.
- Neonatal sepsis.
- Sever malnutrition

Considerations while prescribing antimicrobials:

a. **Dosage:** Calculated in terms of body weights thus in comparison with adults, larger dosage required.
b. **Mode of administration:** has to be parenteral particularly for the neonates.
c. **Duration:** particularly for the neonates, longer duration is required.

Drugs used in:

1. **Pneumonia:** cotrimoxazole, ampicillin, amoxycillin, cephalexin, chloramphenicol, cefotaxime, ceftriaxone.
2. **Diarrhoea:** mostly viral, no antibacterials used.
3. **Dysentery:** cotrimoxazole, nalidixic acid, metronidaazole, furazolodine.

4. **Meningitis:** chloramphenicol, penicillin, ceftriaxone, cefotaxime.
5. **Neonatal sepsis:** penicillin, gentimicin, amikacin, vancomycin.
6. **Malaria:** cholorquine, quinine
7. **Kalazar:** antimony stibogluconate, pentamidine, amphotericin B.
8. **Staph. Skin infections**: cloxacillin, gentamicin,
9. **Severe malnutrition without features of severe sepsis:** cotrimoxazole

Sever malnutrition with features of sepsis:
Ampicillin with gentamicin or chloramphenicol.

Examples of antimicrobials used:

Antimicrobials in bacterial meningitis:

a. **Ceftriaxone:** 100 mg/kg/day in two divided doses Plus vancomycin 60 mg/kg/day in 4 divided doses OR
b. **Cefotaxime:** 200 mg/kg/day in 4 divided doses plus vancomycin, OR
c. **Chloramphenicol:** 100 mg/kg/day in 4 divided doses in patients allergic to B- lactam antibiotics.

Duration of treatment:

Streptococcus pneumoniae:

a. **Sensitive to Penicillin:** Penicillin 300,000 u/kg/day in 4 divided doses for 10-14 days.
b. **Sensitive to third generation cephalosporin:** Ceftriaxone or cefotaxime: 10-14 days.
c. **Resistant to a & b above:** Vancomycine for 10-14 days.

N. meningitides:

a. IV Penicillin for 5-7 days is the drug of choice in uncomplicated cases.

H. influenzae:

a. Ceftriaxone or cefotaxime for 7-10 days.

Listeria monocytogenes:

a. **Ampicillin:** 200 mg/kg/day in 4 divided doses plus ceftriaxone or cefotaxime.

Cases without any identifiable pathogen but with definite evidence of acute bacterial meningitis should be treated with ceftriaxone of cefotaxime for 7-10 days.

E.coli meningitis:

Cefotaxime or ceftriaxone for 2-3 weeks.
P.aeruginosa; Ceftazidine.

Complications of antibiotic therapy:

Phlebitis, drug rash, fever, oral candidiasis and emesis,
Ceftriaxone causes reversible cholelithiasis.

Consider the following questions before prescribing the antimicrobials:

1. **Is it an infectious illness?**
2. **What type of infectious illness is this?**
3. **Is there a laboratory evidence of a particular organism responsible for the infection? Culture? Serology?**
4. **Is there an epidemiological evidence for the organism responsible for the infection?**
5. **Is an antimicrobial indicated?**
6. **In what form? Oral or parenteral?**
7. **Is a single antibiotic effective?**
8. **Is there a need for more than single antibiotic?**
9. **Is the formulation rational?**
10. **What should be the duration of the treatment?**
11. **What are adverse reactions?**
12. **What are the idiosyncratic reactions?**

Anti-microbials in Pregnancy

Dr. P. Pradhan
Professor, Department of Gynecology and Obstetrics, NMC

I. Women commonly ingest medications while pregnant.

- Anti-microbials most commonly prescribed. (antibiotics, antifungal, antiseptics, antiviral)
- Careful in pregnancy: Teratogenic effects.
- Embryonic period (2-8 wks) most critical organogenesis
- Adverse effects in 2nd half of pregnancy e.g. tetracyclines
- Some teratogenicity appear late in reproductive life

II. Anti-microbials use for prevention infection.

- Significant morbidity/adverse outcome – mother, fetus or both.
- Congenital/Neonatal infection avoided: timely treated
- Prophylactic agents – important aspect in obstetrics
- Intervention in obstetrics practice ever increasing.

Antibiotics

III. Drugs: benefit outweigh the risk general/pregnancy

- Antibiotics increasing use – commercial pressure and Bacterial resistance
- Vigilance important – drugs during pregnancy
- Warning "to be used with caution in women of child bearing age"
- Sometimes doctor/patient may not know – pregnant.
- Effects of these drugs on the developing fetus.

Side Effects

- Anaphylaxis in pregnancy as non-pregnancy
- Teratogenic/toxic effects on unborn fetus/neonates
- Effects on early pregnancy by accidents.
- Prescribed; Benefit outweigh the possible risk
- Generally approved antimicrobials are not teratogenic except few

Safer prescribing of antibiotics during pregnancy

- FDA of USA – Classification scheme based on known side effects of drugs.

Table I: FDA Classification of drugs

Category	Description
A	No fetal risk: proven safe for use during pregnancy
B	Fetal risk not demonstrated in animal or human studies
C	Fetal risk unknown: no adequate human studies
D	Some evidence of fetal risk: may be necessary to use drug in pregnancy

Table II: Antibiotics by FDA classification

Antibiotic	A	B	C	D
Penicillins		X		
Penicillin combined with betalactamase inhibitor (e.g. augmentin)		X		
Cephalosporing (e. g. Cefuroxime)		X		
Aminoglycosides (e. g. Gentamicin)			X	
Aminoglycosides (e. g. Streptomycin)				X

Table III: FDA classification of other antibiotics

Antibiotic	A	B	C	D
Chloramphenicol			X	
Metronidazole		X		
Sulphonamides		X		
Tetracyclines				X
Trimethoprim		X		
Nitrofurantoin		X		
Erythromycin		X		

Antibiotics which affect pregnancy

I. **Tetracyclines:** 'D' category (Doxycycline, Minocycline, Oxytetracyclines)

- Board Spectrum bacteriostatic agents
- Act by inhibiting protein synthesis
- Teratogenic in laboratory animals.
- Cross placenta easily
- Complexes with calcium in bones/teeth of fetus during middle to end of the pregnancy.
- Yellow-Brown discoloration of teeth
- Enamel hypoplasia
- Complexes deposited in Fetal long bones
- Inhibition of skeletal growth development in the fetus
- Acute fatty infiltration in pregnant women.
- Secreted in breast milk
- All above and photosensitivity
- Oral/vaginal thrush
- Vestibular disturbances with minocycline
- Congenital cataract.
- Not to be used pregnancy/breast feeding.

II. **Sulphonamides:** 'C' category (Sulphadiazine, Sulphamediozole, Sulphametheoxy pyrimidine).

- Board Spectrum Bacteriostatic.
- Active gram positive/Negative bacteria
- Inhibit the synthesis purine, thymidine and DNA.
- Compete bilirubin for binding to albumin
- Hyperbilirubinaemia causing kernicterus especially in premature neonate.
- High dose – teratogenic – cleft palate
- Secreted in breast milk.
- Not to be used pregnancy/Nursing mothers

III. **Rifampicin:** 'C' Category (antibicterial antimycobacterial, antileprosy)

- Board Spectrum Bactericidal antibiotics.
- Inhibit bacterial RNA synthesis.
- Cross placenta
- Bleeding disorder in mother/infants when administered during last few weeks of pregnancy
- Vit. K indicated

Teratogenicity:

- Imperfecta osteogenesis/embryotoxicity reported in rabbit in high dose.
- Congenital malformation – Cleft palate
  - Spina bifida
- Secreted in breast milk
- No problem documented

IV. **Aminoglycosides:** 'D' Category (Amikacin, Gentamycin, Kanamycin, Streptomycin, Tobramycin)

- Acts by disrupting cytoplasmic membrane and eventual cell death.
- Ototoxitity and Nephrotoxicity.
- Valuable drug "gentamycin" life threatening infection.
- Reserved for Serious maternal infection resistant to other antibiotics.
- Risk: benefit must considered.
- Cross placenta in significant amount
- Bilateral congenital deafness.
- Secreted in milk
- Poor absorb from GIT
- No problems documented in infants.

V. **Chloramphenicol:** 'C' Category

- Bacteriostatic – gram positive/negative/anaerobic
- Bactericidal in high concentration and highly susceptible organisms.
- Act by inhibiting protein synthesis.
- Toxic side effect in mother
  i. aplastic anaemia, bone marrow depression.
- Serious side effects in 3rd trimester
  i. Circulatory collapse of the Neonates (Grey baby syndrome)
- Readily cross placenta
- Child defects not documented
- Not recommended in pregnancy at term/labor
  i. Potential toxicity.
- Secreted in breast milk.
- Bone marrow depression in infant
- Not recommended in Nursing mothers.

VI. **Fluoroquinolones:** 'C' Category (Ciprofloxacin, Norfloxacin, Afloxacin)

- Bactericidal – inhibit bacterial enzyme
- Used in UTI
  i. Norfloxacin - embryonic loss
  - embryocidal
  - not known teratogenicity
  ii. Ciprofloxacin - arthropathy in immature animals.
  iii. Ofloxacin - fetotoxic
  - skeletal anomalies
- Secreted in breast milk
- Not given to Nursing mothers

VII. **Nalidixic acid – gramoneg** 'C'

- Bactericidal / Bacteriostatic: concentration
- Active against most gram Negative Bacteria except (Pseudomonas) that commonly cause UTI.
- Inhibit bacterial DNA synthesis.
- Cross placenta easily

- Arthropathy in immature animals
- Teratogenic/embryocidal in rats
- Prolong pregnancy
- Secreted in breast milk
  i. usually compatible with breast feeding
  ii. hemolytic anemia in G6PD deficiency

VIII. **Nitrofuration:** 'B' Category (Furadantin)
- Bactericidal at therapeutic concentration.
- Inhibit aerobic energy metabolism and synthesis of DNA, RNA, cell-wall protein.
- Uncomplicated UTI in pregnancy
- No congenital anomalies documented.
- Cross placenta
- Term/labor – hemolytic anemia due to immature erythrocyte enzyme in fetus.
- Secreted in breast milk in trace amount
- Hemolytic anemia in G6PD infant.

Safer antibiotics in Pregnancy

I. Penicillin/Amoxycillin 'B' (Amoxycillin, Ampicillin, Cloxacillin, Augumentin)
- Bactericidal.
- Inhibit bacterial cell wall synthesis.
- Well tried and side effects similar to non-pregnant women.
- Augmentin contain beta-lactamase inhibitor – safe in pregnancy.
- Cross placenta easily
- No adverse effects
- Secreted in Breast milk – no problems.
- Sometime sensitization, diarrhea, candidiasis and skin rash seen in infant.

II. **Erythromycin** 'B' (Erythromycin base, Erythromycin estulate, Erythromycin ethylsuccinate, Erythrougen stearate, Erythromycin gluceptate)
- Bactorostatics macrolide antibiotic
- Bactericidal in high concentration or highly susceptible organism.
- Active on dividing organisms.
- Inhibit protein synthesis.
- Use alternative to Penicillin.
- No teratogenic/toxic effect in fetus.
- Erythromycin estolate cause sub-clinical hepatotoxicity in pregnant women.
- Secreted in breast milk – no problem

III. **Cephalosporins** 'B' Category
- 22 brands
- 4 generation of drugs

- Generation classification depends upon spectrum of antibacterial activity.
- Bactericidal – gram positive/negative bacteria. Inhibit bacterial septum and cell wall synthesis.
- Cross placenta easily
- No known adverse effect in the fetus.

- Secreted in breast milk.
- No problems to date.

IV. Antibiotic Prophylactic agents

- Established infection – preventing infection
- Short course, single dose ↓ infection
- Specially tried in prevention of post operative infection following caesarean section.
- Post C/S infection rate 11-85% cf 10% in vaginal delivery.
- Post operative genital tract infection serious complication both immediate and long terms.
- Severe cases – threatens mother's life
- Important increase in the virulence of gr A streptococcus.
- Fatalities after C/S
- Prevention of infection – Policy of routine antibiotic prophylactic.

Risk factors for infection

- Background morbidity of infection at different institution.
- Risk of organism resistance considered with blanket prescription of antimicrobials.

Infection Morbidity

- Varies widely 11-85% after c/S
- Rate differs in institution.
- Rater differs in inclusion criteria.
- Joint committee on maternal welfare.

Febrile Morbidity

- Temperature 38° C or more on 2 occasions of first 10 post operative days excluding the first 24 hours measures at least 4 times a day.

Wound Infection

- Presence of indication, sero sanguineous discharge.
- Dehisence with purulence discharge with or without a positive microbiological culture.

Genital tract infection

Clinical diagnosis:

- Pain / tender uterus
- Purulent discharge from cervix
- Positive microbiological culture no HVS

Urinary tract infection

- Microbiological diagnosis:- $>10^5$/L of organism in a clear catch mid stream urine specimen.

Table IV: Incidence of urinary tract infections in pregnancy

Asymptomatic bacteriuria – 2- 10% of pregnant women 25% will develop symptomatic bacteriuria. Acute pyelonephritis can follow
Acute cystitis – 1% of pregnant women
Acute pyelonephritis – 1-2% of pregnant women 7% develop bacteraemia

- Major risk factor:- Background infection of particular institution.

Table V: Patient at risk for post operative Infection

Emergency Caesarean section
Ruptured membranes >6 hours
Intrapartum infection
Obesity
Prolonged surgery > 1 hour
Anemia
Haematoma formation
Low socioeconomic class
Age <24 years
Induction of labor
Internal fetal monitoring
Previous abdominal surgery

Table VI Common uses of antimicrobials in pregnancy

Condition	Medication	Authors
Caesarean section Prophylaxis	Penicilin or cephalosporin ? Metronidazole	Mallarat et al (1990) Schwarz & Grolle (1981) Duff (1987)
Premature membrane rupture	Antibiotics of little prophylactic benefit	Ohlsson (1988)
Urinary tract infection	Penicillin or cephalosporin	Mc Neely (1988)
Group B streptococci	Penicillin prophylaxis	Tuppurdinen & Hallman(1988)
Chlamydia trachomatis	Chlorhexidine gel Erythromycin Clindamycin/amoxycillin	Kollee et al(1989) Schachter et al (1986) Chrombleholme et al (1990)
Malaria	Chloroquine	Some Plasmodium falciparum-resistant
Neisseria gonorrhoeae	Penicillin or Spectimonycin / cephalosporin	Alternative choices for resistance or penicillin allergy, Chalamydia trachomatis often also present
Acute chrioamnionitis	Broad-spectrum parenteral antibiotics	Treatment to start promptly. No general consensus as to the best antibiotic choice. Gilstrap(1990)
Toxoplasmosis	Spiramycin or Pyrimeth-amine/sulphonamide Combination	For acute infection of fetus Walpole et al (1991)

Antifungal agents

- Vaginal candidiasis common during pregnancy
- Three commonly used agents; Clotrimazole, Micronazole, Nystatin.
- Imidazoles – warning to avoid or use with caution during pregnancy.
- Fluconazoles – Teratogenic. Not used
- Candidal Septicaemia recorded in pregnancy
- 5 Fluorocytosine and ampotoricin – B – Best Therapy.
- Ceriseofulvin:
    - i. mycotin infection – skin nails, scalb
    - ii. areport of conjoined twins
    - iii. CNS anomalies / skeletal abnormalities in off spring
- Caution in pregnancy

Antiviral agents

- Experience with antiviral-limited

1. **Herpes genitalis** – disseminated infection and encephalitis in neonate
   - Elective C/S 4 h membrane rupture with active herpetic lesions
   - Acyclovir treatment mother / neonates.

2. **HIV infection** – Zidovidine
   - Transplacental passage documented
   - Congenital anomalies not increased

3. **Toxoplasmosis** congenital
   - Classical triad – hydrocephalous, chrioretinitis, intracerebral calcification
   - Most cases sub-clinical infection
   - Incidence increases with infection in 3rd trimester.
   - Still severe in first trimester.
   - Incidence 0.5-6.5/1000 live birth
   - Serological screening in early pregnancy to find risk people.
   - Treatment – Spiramycin
   - Intrauterine infection – fetal blood sample and USG

Antiparasitic agents

- Parasitic infection quite common in pregnancy
- Usually asymptomatic – No need of Rx.

Metronidazole

- Vaginal trichomoniasis
- Carcinogenic in rodents
- Mutagenic in certain Bacteria
- No increase in congenital anomdics human
- No teratogenic risk.

Prophylaxis Use of Antimicrobials

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Chemoprophylaxis is frequently successful if a single effective drug is used

i. to prevent infection by a specific microorganism or
ii. to eradicate infection immediately or soon after it is established

Chemoprophylaxis often fails if the aim is to prevent colonization or infection by organism present in the environment.

a. To protect healthy persons from specific organisms to which they are exposed e.g.

- Gr. A streptococci causing acute rheumatic fever-by penicillin G.
- Gonorrhea or syphilis after contact with an infected persons – by procaine penicillin
- E. coli causing recurrent urinary tract infection – by trimethoprim – sulfamethoxazole/ciprofloxacin.
- Meningococcal disease during an epidemic by rifampicin, minocycline or sulfadiazine.

b. To prevent bacterial infection in patients with other disease

- In neutropenic patients e.g. by trimethoprim-sulfamethoxazole or ciprofloxacin or other fluoroquinolones. However superinfections with fungi may occur.
- Prevent endocarditis in patients with valvular disease of heart, in patients undergoing dental, other surgical procedures – appropriate prophylaxis with penicillin or cephalosporin before the procedure.
- Prevent wound infections after various surgical procedures such as involving stomach, pancreas and bowel, however, it should be used in selected operation procedures that involve dirty and contaminated surgical procedures e.g. resection of colon.

c. Conditions in which prophylactic antimicrobials are administrated but the results are by and large unsatisfactory.

- Viral infection of the upper respiratory tract to prevent seemingly bacterial invasion.
- Elective surgery where bacterial contamination of wound is unlikely
- Unconscious patients on respirators.

Misuse of Antibiotics

- Infections of viral etiology
- Fever of undermined origin. The rational approach to treat fever of unknown etiology is to search for its cause and not to unnecessarily expose the patient to chemotherapy in the hope that if one agent is not effective another drug will be effective.
- Administration of insufficient dose for fear of toxicity may result in clinical failures.

- In the presence of pus, necrotic tissue or a foreign body, combination of antimicrobial agent given in addition to surgical removal of the cause.

The antimicrobials in hospital practice are prescribed on clinical judgements alone. Antimicrobial therapy must be individualized on the basis of clinical situation, microbiological report and pharmacological considerations.

Public Health Challenges of AMR

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- Anti-microbial resistance is a day to day problem faced by many clinicians & and microbiologists in an effort to eradicate the overwhelming infections.
- As we have seen many bacteria are becoming resistant to commonly used antimicrobial agents.
- Selection of Resistant mutants began on a global scale in the early 1940's with Penicillin use.
- Thereafter antibiotics & chemotherapeutic agents were introduced to counter the resistance.
- Ways of emergence of bacteria resistance understood.
- To counter b-lactamase activity of the microbes B-lactamase resistant drugs have been discovered & introduced for use
- Now we have 3rd generation cephalosporin group of antibiotics effective against wide range of micro organisms (gram positive & gram Negative).
- Linezolid (oxaZolidionones) is very good that inhibits even the MRSA (Staphylococcus aureus) & streptococcus faecalis (Vancomycin resistant).

Importance

1. Correct identification of resistance early at the onset is important.
2. Helps correct selection of an antibacterial agent for successful eradication.
3. It is necessary to test for each infection as to its Antibiogram pattern.

Anti-microbial sensitivity testing

- Double diffusion method of Kirby Bauer is followed.
- Oxoid discs are used.
- Zone of inhibition is read following NCCLS manuals to interpret sensitivity, Intermediate sensitivity & resistance.
- Measurement is done comparing the findings of the standard ATCC strains of E-coli for gram negative & Staph aureus for gram positive organisms.
- Vancomycin sensitivity test is done to look for sensitivity of Enterococci.

- Oxacillin disc is used for detecting sensitivity Staph. aureus against cloxacillin groups.

- Nitrocefin of Cephalosporings group:- no need to test all first, second & third generation of Cephalosporins. Nitrocefin is used to check for B-lactamase production. It compulsory to check B-lactamase for N. Gonorrhoea for early detection.

- Nalidixic Acid is the weak quinolone & any resistance to Nalidixic Acid indicate possible resistance to Ciprofloxacine.

Emerging anti-microbial resistance problems B-lactamase production is common in members of entrobacteriae & it has been shown that gut flora may be harboring resistance plasmid.

As per our experience followings are the findings.

1. Vibrio cholerae:- Different strains isolated during 1990-1995 were all sensitive to different chemotherapeutic agents except cotrimoxazole. The strains of VC isolated at present are resistant to wider range of drugs such as Ampicillin, Nalidixic Acid & furoxone & Sensitive only to Tetracycline, Erythromycin & Ciprofloxacin.

2. Neisseria gonorrhorea:- Recently we have detected in an young adult with urethritis Penicillin & Tetracycline resistance N. Gonorrhoea. This strain has been referred to ICDDRB, Bangladesh.

3. Salmonella typhi:- We have already come across the strains of Salmonella typhi that are resistant Chloramphenicol (8%). Ampicillin resistance is also common.

4. Luckily we have not come across Vancomycin resistance enterococcus & Oxacillin resistance Staphylococcus

5. Myco-bacterium tubreculosis:- MDR in TB is already a problem in Nepal with increasing problems of HIV/AIDS. TB is common & difficult to treat.

The following precautions have to be taken before saying actual resistance of the microbes.

1. Clinical condition:- like collection of pus, that needs draining.

2. Failure to use the laboratory facility:- culture/isolation & sensitivity testing.

3. Inefficient laboratory personnel due to lack of knowledge.

4. Wrong choice of the drugs

5. Inadequate dose, duration, & wrong route etc.

6. Inappropriate combinations (bactericidal/bacteristatic).

Problems in Developing Countries

1. Over the counter sales
2. Poor package inserts
3. Ignorance of drug sellers and customers.
4. Inadequate dose/duration and inappropriate combinations

Recommendation

1. Proper use of antibiotics
2. Education of HCW and general public
3. Hospital infection control policy
4. Early reporting of any resistance strains
5. AMR monitoring

Surveillance of AMR In Nepal

Focus of attention is on 5 priority pathogens

Respiratory tract

1. H.I.
2. Strep. Pneumoniae

Gastrointestinal Tract

1. Vibrio cholerae
2. Shigella sps.

STD pathogens

1. Neisserie gonorrhoea

The followings are the Antimicrobials recommended for testing in routine AMR works

Pathogen specific list of drugs

Isolate	Antimicrobial agents
1. Vibrio cholerae	Tetracycline Ciprofloxacin Erythromycin Cotrimoxazole] Nalidixic acid
2. Shigellae species	Ampicillin, Ciprofloxacin Cotrimoxazole Nalidixic acid Mecillinam Ceftriaxone

3. Streptococcus pneumoniae	Penicillin Ampicillin, Erythromycin Chloramphenicol Cotrimoxazole Ceftriaxone
4. Haemophilus influenzae	Ampicillin, Chloranphenicol, Cotrimoxazole, Amoxicillin+Clavulanic Acid, Ceftriaxone, Azithromycin.
5. Neisseria gonorrhoea	Penicillin, Tetracycline, Erythromycin, Ampicillin, Ciprofoxacine, Azithromycin, Ceftriaxone, Spectinomycin.
6. Salmonella species	Ampicillin, Chloramphenicol, Ciprofloxacine, Cotrimoxazole, Ceftriaxone, Ceftazidime.

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Public Health Challenges and Use of Anti-microbial Agents in Livestock Production

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1. Introduction

Antibiotics play very import role to overcome bacterial diseases. So, antibiotics are widely used. World wide in livestock production are mainly for three proposes; a. Treatment of disease, b. Prevention of disease and c. for growth promotion. A large amount of drugs are being used world wide annually to secure sufficient quantity of food to feed fast growing population. However, it has been found that indiscriminate use of antibiotics may lead to emergence of antibiotic resistant bacterial population in man and animals.

2. Antibiotic using sectors

Livestock and poultry Production

As therapeutic drugs antibiotics are widely used in treating large animals, poultry and pets in Kathmandu and used all over the country. Accordingly the range of antibiotics used in veterinary practice is very wide and significantly different than in medical practice.

Antibiotics prescribers in Nepal ranges from qualified veterinarians to para veterinary technicians, field assistants to village animal health worker (VAHW), and veterinary shopkeepers. A range of antibiotics, and probiotics are used in veterinary practice for the treatment of animals, poultry and in animal feed production. For the growth promotion effect of such probiotics they have been used throughout the world.

The antibiotics and Probiotics used in animal feeds accelerate growth rate by 10-20 % and reduce feed intake by 2.5% and increase the efficacy of feed conversion by 8.8%. It is claimed that such advantage is achieved through regulating growth of desired species of bacteria and increasing absorption capacity of intestine. The growth promoters used in livestock production in USA and other countries are given in table 1 and antibiotics commonly used as feed additives in Nepal is given in table 2.

Table 1: Type of Antibiotics and Probiotics used as feed additives in USA.

Compound	Class	Absorption	Used in animal species
Zinc bacitracin	Peptide	Not absorbed	Poultry
Flavomycin	Phosphoglycolipid	Not absorbed	Poultry and Cattle
Virginiamycin	Peptide	Not absorbed	Poultry
Avoparcin	Alycopeptide	Not absorbed	Poultry, Pig and cattle
Lasalocid sodium	Ionophore	-	Cattle
Monesin sodium	Ionophore	Poorly absorbed	Cattle, lambs
Salinomycin	Ionophore	-	Animals and birds.

Source: The Merk Vet. Manual, 1998

Table 2: Antibiotics commonly used as feed additive in Nepal.

Antibiotics	Imported quantity (MT per year)*	Concentration used in feed
Oxytretracycline	39-44	100g/mt
Tretracycline	1-11	NA
Doxycycline	2-4	100g/mt
Bacitracin	1-2	10-20g/mt
Furazolidone	2	5g/mt

* Approximate figures, DLS records.

3. Antibiotics in Use

The use of antibiotics is considered essential for the efficient production of foods of animal origin (WHO, 1985). With the advent of modern antibiotics the prevention and treatment of disease of food producing animal has advanced significantly (WHO, 1985). Because of their beneficial action, a large amount of antibiotics are used for animals worldwide. The world production of antibiotics by 1980 had reached more than 25,000 tons of which large proportion was used in feed (Timoney et. al., 1988). Liss and Batchelor (1987 as cited by Prescott and Baggot, 1993) mentioned that the sales of antibiotics worldwide are expected to exceed $ 40 billion by the year 2000. In the United States, more than 40% of all antibiotics produced are used for animals (Stalheim, 1987). Correspondingly, more than 80% of the meat and eggs consumed by the public have been produced with the aid of medicated feeds in the United States (Marteniuk et.al., 1988). In Japan more than 60% of all antibiotics used to treat food producing animals and poultry are tretracycline (Tsi and Kondon, 1994). However, in Nepal, the situation on the use of antibiotics in animal production has not been studied thus the situation is not known.

The increasing world population presents a growing challenge to secure sufficient quantities of food of animal origin. This challenge needs to search for new ways of enhancing productivity of food animal husbandry. This demands the use of antibiotics for disease prevention, treatment and growth promotion. Prophylactic use of antibiotics occurs before signs of disease become evident to avoid clinical disease where as therapeutic use aims at minimizing the economic loss due to the disease. The commercially raised bird is exposed to infectious agents for most of its life yet may only exhibit clinical signs of disease when subjected to additional stress such as vaccination, ambient temperature, excessive ammonia (>25ppm) transport, mycotoxins in feed, change in diet, anthelmentic administration, etc. (Tanner, 1993).

It is generally accepted that certain antibiotics such as penicillin, virginiamycin, bambermycin, avoparcin, bacitracin, etc. are capable of stimulating the growth rate or feed efficiency or both. Thus feeding of antibiotic mixed rations to animals is practiced widely in many parts of the world. In the United States, many antibiotics are incorporated in feed at low levels to promote growth and protect against disease (Tanner, 1993). The increased benefit from using sub-therapeutic levels as growth promoter could be seen under conditions which impair growth, such as unclean and crowded environments and marginal ratios. In a study, Spee (1982 as cited by Steele and Beran, 1984) stated that chicken increased up to 12.2% in weight gain and 7.1 % feed

efficiency up to 4 weeks of age and growing pigs showed 15 % increase in weight gain and 5 % improvement in feed efficiency.

Mixing of 20 ppm antibiotics with feed does not give rise to drug residues in food. However, feeding 100-200 ppm antibiotics may result in residue in food and in residue in food and development of antibiotic resistant organisms (WHO, 1969).Thus good animal husbandry practices such as clean environment, timely immunization and anthelmintic administration should be practiced as far as possible instead of using antibiotics.

Rational use of antibiotics

Regulatory measures may help for proper use of antibiotics in animals and humans and to avoid their residues in foods of animal origin. In developing countries farmers, practitioners, consumers and the general public may not be aware of the misuse of antibiotics in animal production and its consequences. The following sectors can play important roles for the proper use of antibiotics in animal production.

Role of animal raisers

Poultry raisers should follow label directions of the antibiotics. Management factors such as observance of withdrawal period, proper recording and identification of treated birds and animals would help to reduce or avoid residue problems (Kaneene. 1987) Use of drugs only when it is necessary and according to the approved route species of animal, age and stage of production of the animal may help to avoid misuse of antibiotics.

Role of feed manufacturers

If feed manufacturers need to mix antibiotics in feed as growth promoter, proper selection and dosing is important.

Role of veterinarians

Veterinarians have responsibilities to protect the health of the animal and to protect public by assuring that animal and animal product entering into the food chain is safe. They should avoid as far as possible unnecessary use of antibiotics. They can choose, decide dose and route of administration of antibiotics. They can educate the farmers about the necessity of withdrawal period.

Role of the government

Government can enhance the proper use of antibiotics by formulation and implementation of policies, rules and regulation. Government can also play a role to coordinate and educate all of the related agencies and organizations for proper use of antibiotics.

Role of pharmaceutical industry

Proper labeling of antibiotics mentioning dose rate, route of administration, withdrawal period is important. This would help to reduce or avoid improper use of antibiotics.

Awareness

Awareness among the drug users, practitioners, feed and drug manufacturers about the proper use of antibiotics and consequences of misuse should be created by training, workshop/seminar and discussion.

Conclusion and recommendations

It is evident that antibiotics are required for efficient animal production. Benefits of use of antibiotics in animal production are distinct where as there are still controversies on their ill effects. The use of it, however, should not be done indiscriminately. They should be used only when they are required. The products from animals are not unsafe for consumption until it cross the acceptable daily intake (ADI) and maximum residues level (MRL). Resistant bacteria may develop even without the use of antibiotics but indiscriminate use may lead to further emergence.

Producers, practitioners and feed manufactures can play important role for proper use of antibiotics. Thus, educational efforts to them should be provided. Surveillance of antibiotic resistance and sensitivity test before use of antibiotics should be done for proper selection of antibiotics.

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Annex 2

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6.	Dr. Kamal Lamsal	TUTH
7.	Dr. Prakash Subedi	Pathan Hospital
8.	Dr. Pabina Rayamajhi	Kathmandu Medical Collage
9.	Dr. Rajib Jha	Bir Hospital
10.	Dr. Sita Sharma	TUTH
11.	Dr. Sharad K. Sharma	Patan Hospital
12.	Dr. Sundar Hyoju	Birendra Police Hospital
13.	Dr. Srikrishna Bhatta	Bir Hospital
14.	Dr. Sudarshan Lal Dhanju	SGN Heart Center
15.	Dr. Sushapana Hirachand	Maternity Hospital
16.	Dr. Sagun Shrestha	Nepal Medical College
17.	Dr. Sonu R. Thapa	Nepal Medical College
18.	Dr. Eva Gauchan	Nepal Medical College
19.	Dr. Sunil Mani Pokharel	Kanti Children's Hospital

Annex 3

Training on Rational Use of Antimicrobials to the Fresh Medical Graduates and House Officers

Program

21 Jan 2002

11:30 A.M. – 12:30 PM – Introduction of the participants and of training + Pre-training evaluation

12:30 – 1:00 PM – Tea Break

1:00 – 2:00 PM – Principles of anti-microbial selection and use – host factor; host defense mechanism
Dr. Basista Rijal

2:00 – 4:00 PM – Principles of anti-microbial selection and use- pharmacokinetic, pharmacodynamic and pharmacogenetic factors
BB Thapa
SP Lohani

4:00 – 4:15 PM – Tea Break

22 Jan 2002

11:30 – 12:30 PM – Science of AMR – definition, resistance mechanism, transfer resistance (cross resistance), and value of microbiological diagnosis
Dr. VL. Gurabacharya

12:30 – 1:00 PM – Tea Break

1:00 – 2:00 PM – Epidemiology of infectious disease: Disease prevalence
Dr. IL. Acharya

2:00 – 3:00 PM – EHP (USAID/MOH) Programme on Prevention and Control of Vector Borne Diseases in Nepal
Dr. P. Wijeyaratne

3:00 – 4:00 PM – Regulatory measures
RR Prasad

4:00 – 4:15 PM – Tea Break

23 Jan 2002

10:30 – 11:30 PM – Use of two or more antibiotics, advantages and disadvantages of use of multiple antibiotics.
Dr. K.K. Kafle

11:30 – 12:00 PM – Tea Break

12:00 – 1:00 PM – Use of antimicrobials in children.
Dr. R.K. Adhikari

1:00 – 2:00 PM – Use of antimicrobials in pregnancy
Dr. Pramila Pradhan

2:00 – 3:00 PM – Prophylactic use of antimicrobials, Antimicrobials in eldery
Dr. K.K. Kafle

3:00 – 4:00 PM – Public health challenges due to AMR
Dr. Chandrika Shrestha
Dr RM Shrestha

4:00 – 4:30 PM – Post-training evaluation.

4:30 – 4:45 PM – Tea Break