



Selections from Drug & Therapeutics Letter*

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MULTI-DRUG RESISTANCE: A GREAT THREAT

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Antimicrobial resistance (AMR) was first reported in the early 1940s (streptococci and gonococci resistant to sulphonamides). Since then many cases of AMR have been reported. It has now become a serious global problem with the emergence of **multidrug resistant** (MDR) variants of pathogens.

There is no consensus about the definition of multidrug resistance. Some consider an organism as MDR if it is resistant to at least four of a group of six listed drugs. Some define this as resistance to usually employed drugs. And some define it as resistance to two or more drugs to which the bacteria are usually susceptible.

Resistant and multiresistant microbes are an important cause of **hospital-acquired**

infection. Infections associated with such organisms can pose a serious threat to vulnerable patients such as neonates, cancer patients and those who are immunocompromised, debilitated, or elderly. Intensive care units (ICUs), burn units, high-dependency units and infectious disease care centres generally make frequent use of antimicrobial agents, resulting in great likelihood of resistance and multiresistance. Methicillin-resistant *Staphylococcus aureus* (MRSA), *Enterococcus faecium*, *Enterococcus faecalis*, *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter* spp, *Citrobacter* spp, *Pseudomonas aeruginosa* and *Acinetobacter calcoaceticus* have become important hospital pathogens. These pathogens can complicate treatment, increase morbidity and mortality, delay discharge and increase the cost.

MRSA is a well-known cause of nosocomial infections. Some MRSA strains are resistant to all antimicrobials except the glycopeptides — vancomycin and teicoplanin. Sometimes the only active agent is

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vancomycin. The fact that *S aureus* with intermediate-level resistance to vancomycin (VISA) has been reported in Japan, USA and France is extremely alarming. VISA tends to emerge in patients who have received multiple courses of vancomycin, is difficult to detect by conventional laboratory procedures, and has been associated with treatment failures. VISA infection leaves very few therapeutic options. To prevent the spread of VISA, it is extremely important that vancomycin be used only when there is no alternative.

Enterococci, which are commensal flora of the intestinal and genital tracts, are rising as hospital pathogens. Their natural resistance to most commonly used antibiotics and their capacity to acquire resistance to other antibiotics have helped them to emerge as nosocomial pathogens as a result of inhibition of other sensitive microbial flora by antibiotics. Enterococci can cause endogenous urinary tract and wound infections, bacterial endocarditis, bacteraemia, meningitis, and other invasive infections in immunocompromised patients (especially those in ICUs and transplant, dialysis and oncology units). Treatment of serious enterococcal infection with synergistic combinations of an aminoglycoside and a beta-lactam or a glycopeptide has now been weakened by high-level aminoglycoside resistance (in about 26% of endocarditis isolates). Glycopeptide-resistant enterococci have been isolated from sewage and farm animals. Use of avoparcin (also a glycopeptide) in agriculture contributed to the emergence of glycopeptide-resistant enterococci. Use of vancomycin and

cephalosporins in hospitals has also increased selection pressure for glycopeptide resistance.

Enterobacteriaceae produce beta-lactamases. Newer beta-lactams were developed to resist bacterial beta-lactamases. But, Gram-negative bacteria with extended-spectrum beta-lactamases (ESBLs) have evolved. About 25% of *E coli* isolated from blood and CSF are now multiresistant (to four or more agents). Twenty to 40% of enterobacter and citrobacter are resistant to all beta-lactams except carbapenems (imipenem and meropenem) and tomosillin. ESBL-producing multiresistant strains of *K pneumoniae* have caused major outbreaks of infection in the hospitals of UK. ESBL-producers are mostly resistant to ceftazidime, ceftriaxone and aztreonam. These are also usually cross-resistant to aminoglycosides and ciprofloxacin. Although most of the clinically important gram-negative bacteria have remained susceptible to carbapenems, recently microorganisms have been isolated which produce carbapenemases that confer high-level resistance to all beta-lactams including carbapenems.

Salmonella typhi that are multi-resistant to chloramphenicol, ampicillin, trimethoprim, streptomycin and sulphonamides have become a big problem in endemic areas of the world. In Quetta, Pakistan, 69% of *S typhi* isolated from blood were multidrug resistant. The growing problem of resistance can also be noted from the fact that chloramphenicol-resistant isolates rose from about 1% in 1989 to 35% in 1994 in the UK. Resistance to ciprofloxacin is also appearing. In fact, multiresistant strains of *S typhi* with

resistance to ciprofloxacin have already caused major outbreaks of typhoid fever in Asia.

Shigella spp., a major cause of acute invasive and fatal diarrhoea in some developing countries, has become multi-resistant to ampicillin, tetracycline, trimethoprim and sulphonamides. In England and Wales, as high as 70% of *Shigella spp.* isolates are reportedly resistant to four or more antibiotics.

Neisseria meningitidis, which has caused large outbreaks of meningitis in sub-Saharan Africa, has developed intermediate resistance to penicillin. Transmissible high-level resistance to chloramphenicol, sulphonamides and streptomycin in its type B strains has been reported in France and Vietnam. *Neisseria gonorrhoeae* is already frequently resistant to sulphonamides, penicillins and tetracyclines. Now its resistance to fluoroquinolones has also emerged, and thus in some areas gonorrhoea can be reliably managed only with third-generation cephalosporins.

Pneumococcus is a major cause of community-acquired pneumonia, otitis media and bacterial meningitis. The resistance of this organism to penicillin is a matter of major concern all over the world. Penicillin-resistant pneumococci are also more likely than penicillin-sensitive ones to be multi-resistant to macrolides, chloramphenicol, tetracyclines and cotrimoxazole.

WHO has declared **tuberculosis (TB)** a global emergency. Multidrug-resistant TB (MDR-TB) and association of TB with human immunodeficiency virus (HIV) infection have challenged TB control efforts. While primarily resistant TB can be there in the community,

an acquired resistance develops in a person previously exposed to inadequate or inappropriate treatment. Directly Observed Treatment, Short Course (DOTS) has been implemented to improve outcome. But even DOTS is not effective in areas where MDR-TB is prevalent, and "DOTS-plus", which calls for close monitoring and more commitment from community, has been proposed. Treatment of MDR-TB often involves prolonged courses of second-line drugs. Even with the best of treatment, there is only 50% chance of cure of MDR-TB and the cost of therapy of such cases can be up to 50 times higher than the cost of treatment of non-resistant TB with standard short course chemotherapy.

In its short history of just about two decades, **HIV infection** has become one of the biggest epidemic threats. Resistance has already been seen to all types of anti-HIV drugs (nucleoside analogue reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, and the protease inhibitors). Even expensive treatments with combinations of three or four anti-HIV drugs have commonly faced failures. Besides poor patient compliance associated with expense of drugs and other factors, resistant virus is an important factor for such failures.

Influenza viruses are frequently resistant to amantadine. Resistance of **herpes virus** to acyclovir has been observed in immunocompromised patients such as AIDS patients or recipients of bone-marrow transplants. Resistance to gancyclovir can also occur in such patients if they are on prolonged treatment with this drug for cytomegalovirus infection.

Azole-resistant isolates of ***Candida albicans*** and ***Candida glabrata*** have been isolated from AIDS patients with oropharyngeal candidiasis. Failure of amphotericin B to penetrate the fungal cell wall of some resistant species has also been suggested.

Attempts to eradicate **malaria** in 1950s failed, primarily due to the emergence of resistance to insecticides and antimalarial drugs. Since 1960 malaria transmission has risen in endemic areas and multidrug-resistant strains of *P. falciparum* have spread. MDR in malaria now extends to chloroquine, pyrimethamine-sulfadoxine, quinine, mefloquine, and halofantrine. More recently, chloroquine-resistant strains of *P. vivax* have also emerged.

Leishmaniasis affects over 10 million people in the world. About 1% of the cases are resistant to the antimonial drug — sodium stibogluconate. Some patients do not respond to both antimonials and pentamidine.

Many countries and organisations have voiced much concern over the issue of antimicrobial resistance (AMR). This problem constitutes a major threat to public health and effective actions are urgently needed to control it.

Resistance emerges from unprudent over-utilization of antibiotics trying to sterilize the environment. Under-treatment can also be responsible. Excessive and inappropriate uses of antibiotics are reported even in countries where antibiotics are available only on prescription. In many developing countries, antibiotic use is unregulated and prescribing is often inappropriate. Free availability and self-medication of antibiotics,

lack of or difficult access to health facilities, inadequate public awareness, uncontrolled antibiotic use in agriculture, lack of adequate AMR surveillance, and lack of updated national antibiotic policies and guidelines are added worries in our context. Antibiotics are commonly used in animals for prophylaxis or as performance enhancers. Such usage does not attain therapeutic levels and is likely to increase the development of resistance. Human factors such as international travel, movement of patients from hospitals to community, improper disposal of infectious wastage, and unhygienic behaviours contribute to fast spread of AMR as well as infectious diseases.

Recommendations for slowing of AMR

The following practices may be helpful to slow down the emergence and spread of AMR problems:

1. Formulating evidence-based national and local antimicrobial use guidelines and effectively implementing such guidelines.
2. Carrying out comprehensive and strategic AMR surveillance at local and national levels. The findings should be used to track the changes in resistance, and identify areas of weakness in infection control policies, and support local formularies and antimicrobial prescribing policies.
3. Improving diagnostic technologies for rapid identification of bacterial and viral infections.
4. Avoiding antibiotic use for trivial infections that would resolve without antibiotic intervention.

5. Avoiding sub-therapeutic doses of antibiotics in humans.
6. Controlling or banning of those antibiotics in agriculture and veterinary practice that have possibility of cross-resistance with antimicrobials in human use. Also the use of other antibiotics as growth promoters and performance enhancers should be discouraged.
7. Developing and adhering to local formularies.
8. Applying rotational use of antibiotics where appropriate.
9. Keeping antibiotic courses as short as possible with coverage as narrow as possible.
10. Limiting surgical antimicrobial prophylaxis to the perioperative period.
11. Reserving particular antibiotics for resistant cases, and making these antibiotics available only on prescription. Auditing and feedback of the use of these agents.
12. Establishing active infection control committees involving clinical microbiologists, clinical pharmacologists, clinical doctors, hospital pharmacists & nurses.
13. Adhering to handwashing recommendations and barrier precautions.
14. Improving hygienic measures in kitchen, hospitals, schools, and water supply to prevent the spread of resistant organisms.
15. Giving greater emphasis on infectious diseases and antimicrobial therapy in undergraduate and postgraduate level medical, pharmaceutical, and nursing educations.
16. Providing effective public education to encourage better understanding about appropriate antibiotic use and to deter inappropriate demand for antibiotics.

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MECHANISM OF DRUG RESISTANCE

Contributed by **Dr B. M. Pokhrel**, PhD, Department of Microbiology, Maharajgunj Campus and TU Teaching Hospital, Institute of Medicine, Maharajgunj, Kathmandu.

Different ways by which anti-microbials can act on bacteria are as follows:

- Inhibition of cell wall formation, which leads to cell lysis (examples - penicillins, cephalosporins, vancomycin).
- Damage of the bacterial cell membrane, which leads to loss of contents and then death (examples - polymyxins, amphotericin B).
- Inhibition of protein synthesis, leading to the arrest of bacterial growth (examples - aminoglycosides, tetracyclines, erythromycin, chloramphenicol).
- Inhibition of nucleic acid production, leading to prevention of bacterial reproduction (examples - nalidixic acid, rifampicin).
- Blockade of metabolic pathway (examples - sulphonamides, trimethoprim).

Resistance to antimicrobial drugs

There are different mechanisms by which micro-organisms may develop resistance to drugs.

1. *By producing enzymes that destroy the active drug.*

Bacterial strains that produce betalactamase (penicillinase) are resistant to betalactam group of antibiotics, eg, betalactamase-producing *Staphylococcus aureus* destroys penicillin G. Similarly, penicillinase-producing *Neisseria gonorrhoeae*

hoeae is resistant to penicillin. Gram-negative bacteria that produce adenylating, phosphorylating or acetylating enzymes can destroy aminoglycosides.

2. *By changing permeability to the drug.*

Tetracycline is accumulated in susceptible bacteria but not in resistant ones. Resistance to polymyxins is also associated with a change in drug permeability. Streptococci possess a natural permeability barrier to aminoglycosides. Resistance to amikacin and to some other glycosides may be due to lack of permeability to the drugs, which is because of an outer membrane change that impairs active transport into the cell.

3. *By altering the structural target for the drug.*

Chromosomal resistance to aminoglycosides is associated with alteration or loss of a specific protein in the 30s subunit of the bacterial ribosome that serves as a binding site in susceptible organisms. Erythromycin-resistant microbes have an altered receptor on the 50s subunit of the ribosome that results from methylation of a 23s ribosomal RNA.

4. *By developing an altered metabolic pathway which bypasses the reaction inhibited by the drug.*

Some bacteria resistant to sulphonamide do not require extracellular PABA but, like mammalian cells, can utilize preformed folic acid.

5. *By developing an altered enzyme which can still perform its metabolic function.*

In trimethoprim-resistant bacteria, the dihydrofolic acid reductase is inhibited much less efficiently than in trimethoprim-susceptible bacteria.

Origin of drug resistance

There are two types of drug resistance: primary and acquired.

Primary resistance is due to inherent property of bacteria resistant to certain drugs, such as penicillin-resistant *E. coli*.

Acquired resistance is due to *gene transfer* or *mutation* from one bacterium to another, which can be either chromosomal or plasmid-mediated. This can happen both within and outside the species.

Non-genetic origin

Usually Log Phase of bacterial growth is required for most antibacterial drug actions. Bacteria that are metabolically inactive (non-multiplying) may be phenotypically resistant to drugs. However, their offsprings are fully susceptible. For example, after infection, mycobacteria often survive for many years in tissues in dormant (non-multiplying) form. Such persisters are resistant to treatment and cannot be eradicated by drugs. Yet if they start to multiply (eg, following suppression of cellular immunity in the patient), they become fully susceptible to the same drugs.

Bacteria may lose specific target structure for a drug for several generations and thus become resistant. For example, L-form bacteria are resistant to penicillin and may remain so for many generations. When these

organisms regain their cell wall, they again become susceptible to penicillin.

Figure: Genetic origin of drug resistance.

Genetic origin

Organisms may develop resistance as a result of genetic change and they increase in number by subsequent selection pressure through antimicrobial usage.

A. *Chromosomal resistance:*

This is associated with spontaneous mutation at a locus that controls susceptibility to a given drug.

B. *Extra-chromosomal resistance:*

Plasmids are extrachromosomal genetic materials. All bacteria may not necessarily contain plasmids. Plasmids are by nature unstable. They play a vital role in gene transfer. R factors are a class of plasmids that carry genes for resistance to one or several antibiotics and heavy metals. Plasmids often control the formation of enzymes capable of destroying antimicrobial drugs. For example, plasmids that carry genes for the formation of betalactamases determine resistance to penicillins and cephalosporins. Other examples are plasmids that code for enzymes which destroy chloramphenicol (acetyltransferase), for enzymes that acetylate, adenylate or phosphorylate various aminoglycosides, and for enzymes that determine the active transport of tetracyclines across the cell membrane.

Genetic elements including plasmids can be transferred by the following **mechanisms** (see figure):

1. **Conjugation** (through cell to cell contact). This mechanism is mediated by a fertility factor (F). Transfer of DNA occurs from donor (F+) cell to recipient (F-) cell. This is the commonest method by which *multidrug resistance* spreads among different Gram-negative bacteria. Transfer of plasmids occurs among Gram-positive cocci as well.
2. **Transduction.** Bacteriophage is a virus that infects bacteria. Gene enclosed in a bacteriophage is transferred to another bacterium, eg, the plasmid carrying the gene for betalactamase production can be transferred from penicillin-resistant *Staphylococcus* to penicillin-susceptible *Staphylococcus* by bacteriophage through lysogenisation process.
3. **Transformation.** Naked DNA can pass from one cell of a species to another cell, thus altering its genotype.
4. **Transposition.** Short DNA sequences can be transferred from plasmid to plasmid or from plasmid to a portion of bacterial chromosome within a bacterial cell.

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TUTH FORMULARY 1997

The Tribhuvan University Teaching Hospital (TUTH) Formulary was published in November 1997. It includes 371 drugs. There are, however, a total of 617 dosage forms. There is a separate Emergency Drug List within the Formulary, which includes 89 items. Classification of drugs in the TUTH Formulary follows the same pattern that is used in the WHO Model List of Essential Drugs and the National List of Essential Drugs of Nepal.

The TUTH Formulary was developed in a participatory manner. First, the TUTH Drug Sub-Committee formed a Formulary Committee, which was approved by the Hospital's Director. The Formulary Committee prepared a draft formulary. It was circulated to advisors, who were identified by the Drug Sub-Committee and endorsed by the Hospital Director. There were altogether 27 advisors, representing heads and unit chiefs of the different departments plus other resource persons. All the advisors were provided with a copy of the draft formulary with a request to discuss with colleagues within their departments/units and provide inputs. The formulary was then revised and finalised after

incorporating the comments and suggestions provided by the advisors. The Formulary is indexed.

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NEW CLASS OF ANTIMICROBIAL AGENTS

Human beings have developed and used several classes of antibiotics in the present century. Microbes have also devised methods of creating resistance to antimicrobials and in recent years there has been a disturbingly large increase in the problem of anti-microbial resistance (AMR). To combat this problem, reforms at the clinical and strategic level are extremely important. At the same time, development of new anti-microbial agents is also an important need.

New antimicrobials can be developed in three main ways:

- (1) modification of the already existing agents,
- (2) genome approach, and
- (3) development of vaccines.

Recent development of **newer fluoroquinolones** such as trovafloxacin, grepafloxacin and moxifloxacin is an example of extension of antibacterial spectrum of the existing agents. These agents are active against ciprofloxacin-sensitive gram-negative organisms and, in addition, have improved anti-pneumococcal activity. Trovafloxacin is also active against anaerobic bacteria.

Compounds called **streptogramins** have been used by the veterinary profession.

Recently they have been found to be useful in the treatment of gram-positive human infections. A mixture of two streptogramins - quinupristin and daltopristin (Synercid) - has been shown to be effective against enterococci, streptococci and staphylococci, including MRSA.

Avilamycin has commonly been used as a growth promoter in animals. A closely related group of compounds called **everninomycins** are under investigation for human use. They have been found to be active against streptococci, staphylococci and enterococci.

Another group of compounds called **oxazolidinones** is also under investigation for human use. Linezolid is one such compound. Oxazolidinones show activity against pneumococci, enterococci and staphylococci, including MRSA.

Another area of interest is **genomic approach**. In recent years, genomic sequencing of many bacterial species has been under-taken. This provides possibility for identification of novel bacterial targets related either to bacterial growth or to the infectious process. For example, the enzymes aminoacyl t-RNA synthetases, which are essential for the synthesis of proteins in bacteria, could be one such target and compounds inhibiting these enzymes could become novel antimicrobial members.

Many animals produce **short chain peptides** as defence mechanisms. Some of such agents have been isolated from the skin of frogs and from insects and pigs. Magainin is a short chain peptide that is being clinically investigated as a broad-spectrum topical antimicrobial agent.

Another possibility is development of **vaccines** for infections in which the problem of resistance is increasing. Under current investigation are vaccines against group

B meningococcus and human immuno-deficiency virus.

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READING CLINICAL TRIAL REPORTS CRITICALLY

In recent decades there has been a great explosion of bio-medical information. It is estimated that about 20,000 biomedical journals exist in the world and about 17,000 scientific and technical articles are published every day. Similar to the literature in other biomedical areas, the literature related to drugs and therapeutics has also undergone huge proliferation in recent decades.

Literature on drugs and therapeutics can be primary (eg, original articles), secondary (eg, abstracting services) and tertiary (eg, books). Of these, the most important is primary literature that includes research-based papers such as reports of clinical trials on drugs.

The quality and dependability of different trial reports can vary. We cannot correctly assess the quality of a publication unless we develop the skill of reading and evaluating it critically.

A report may have been presented in an attractive manner but it may be biased or contain unsubstantiated opinions. There may also be inaccurate statements. Therefore, an important responsibility is to assess the reliability of the report before it is utilised. There are many drug-related papers that are published for promotional

purposes. In such papers there may be unjustified or exaggerated claims about efficacy but glossing over of untoward effects.

Given below is a checklist that can help evaluate a clinical trial report for its usefulness and validity.

Title	<ul style="list-style-type: none"> - Is it accurate, clear and meaningful? Does it reflect the content of the paper? - Recheck the title for its appropriateness after you have read the whole paper.
Authors	Who are the authors? Which 'units' or 'institutions' have they published from? What is their general reputation?
Journal	How credible is the journal nationally and internationally? Is it peer-reviewed? How extensively is it indexed?
Abstract	Are the following included in the synopsis or the abstract - objective, design, setting, patients/participants, interventions (if any), main outcome measures, results and conclusion?
Introduction	Is there a brief review of the available literature? Does the question being asked in the study logically flow from the available literature and evidence?
Methods	<ul style="list-style-type: none"> - What method was applied? Was it suitable in relation to the objective of the study? Is it an established method with acceptable precision? - Who were involved in making the measurements? Were they trained and well-suited for the purpose? - How were the samples selected? Were subjects matched in terms of age, sex, weight and race? What were the inclusion and exclusion criteria? Were "control subjects" used? If yes, what type of controls were used (placebo or active drug)? - Was the disease well-defined? What were the diagnostic criteria? - Which technique was used (parallel group or cross-over)? If a "cross-over" trial was used, was adequate "wash-out" period interposed between two treatments to prevent carry over effects? If cross-over trial was used, was the disease suitable for such a design? (Cross-over trials are suitable only if the disease is chronic in nature and does not undergo spontaneous changes in its severity.) - If a new drug was being compared with an already established drug used for the treatment of the disease in question, was the latter used in an accepted therapeutic dose? Or was it used in a sub-optimal dose?
Results	<ul style="list-style-type: none"> - Are the results easily understood? Are the data clear or are they ill-sorted? - If present, are the graphs and tables appropriately labelled? Are they consistent with the text? - Is there any reference to statistical analysis? If yes, was the statistical test applied appropriate for the type of study? - What was the type of analysis ("analysis by intention-to-treat" or "analysis of the compliers only")?
Discussion and Conclusion	Is the discussion logical and methodical? Does it cover all the aspects relevant to the study? Is comparison made with already existing reports, if relevant? Does the conclusion drawn appear justifiable? Or, is there over-inference? Does it appear biased?

Bibliography	Are references provided for important statements made in the paper? Are the references quoted from reputed sources or from some obscure sources? Are the references given in full? Are they presented in standard formats (for example, Vancouver System or Harvard System) ?
Declaration	Are declarations made about sponsorship or grants, if any? Are there declarations about associations or relations, if any, with any organisation (including drug industry), that could otherwise be interpreted as "conflict of interest" if not declared?

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DRUG DOSING IN PATIENTS WITH RENAL DISEASE

Kidney is the major organ of elimination of many drugs and renal disease can have significant influence on drug excretion. It is therefore important to assess renal function before prescribing drugs eliminated through this route.

Creatinine clearance generally gives an idea about the status of renal function. In daily practice, creatinine clearance is conveniently estimated from serum creatinine. This can be done by using the equation of *Cockcroft and Gault* (1976). The equation, which takes into consideration the age, body weight and sex of the patients, is as follows:

$$Cl_{Cr} \text{ (men)} = \frac{(140 - \text{age}) \times \text{ideal body weight (kg)}}{72 \times \text{serum creatinine (mg/dl)}}$$

Where,

Cl_{Cr} = Creatinine clearance (ml/min)

For women, the result should be multiplied by 0.85.

Conversion between conventional units of serum creatinine (mg/dl) and SI Units (micromol/litre) can be done as follows:

$$1 \text{ mg/dl} = 88.4 \text{ micromol/litre.}$$

In patients with changing kidney function, serum creatinine should not be used to estimate clearance. In such patients the estimation should be based on timed urine collection. Creatinine clearance based on serum creatinine can also be erroneous in the elderly or those with decreased muscle mass. Such patients can have reduced renal function even in the presence of "normal" serum urea or creatinine.

Different methods of dose calculation in renal impairment (eg, nomogram, drug tables, computer-assisted dosing recommendations) should be taken only as an initial guide and not as a fixed approach to therapy. Adjustment of subsequent dosage should be based on regular monitoring of clinical response and plasma drug concentration.

The loading dose of a drug in patients with renal dysfunction is generally the same as the initial dose in patients with normal renal function. Modification is, however, needed in subsequent maintenance dosing schedule. This can be done either by increasing the interval between the two doses or by decreasing the size of the dose. The former method, which is convenient and cost-

effective, is suitable for drugs with large safety margin and long half-lives. The method of reducing dose while keeping the dosing interval unchanged is suitable for drugs that have narrow therapeutic margin and short plasma half-life. This method provides a more constant plasma concentration of the drug. A policy that combines both of the above methods, ie, dose reduction as well as prolongation of dosing interval, often works out to be effective and convenient.

It is important to calculate the fraction of normal dose that is to be used for maintenance dosing. This can be done in the following way:

$$\text{Dose fraction} = \frac{F}{[(Cl_{cr}/120) - 1] + 1}$$

Where,

F = fraction of the drug excreted unchanged in the urine, and

Cl_{cr} = creatinine clearance.

If F is not known, then the dose fraction can still be calculated in the following way:

Dose fraction =

$$\frac{\text{drug t}_{\frac{1}{2}} \text{ normal}}{\text{drug t}_{\frac{1}{2}} \text{ renal failure}} [(Cl_{cr}/120) - 1] + 1$$

The dose fraction helps in knowing the amount of each individual dose to be reduced. The same dose fraction can also be utilised for dosing interval prolongation methods. This can be done in the following way:

Dose interval in renal insufficiency =

$$\frac{\text{Normal dose interval}}{\text{Dose fraction}}$$

Nomograms are also available for graphic determination of individual drug clearance fraction of a drug in a patient with renal failure.

Some drugs are removed significantly by hemodialysis. A post-dialysis supplemental dose is required to maintain adequate therapeutic concentration of such drugs. But for some drugs there is no need for dose adjustment with dialysis because they are not removed significantly with this process.

After a drug is started in a patient with renal impairment, careful and close monitoring is extremely important. The status of renal function must be determined regularly throughout the treatment period. Clinical evaluation for drug efficacy and toxicity should be continually carried out. Regular monitoring of plasma concentration is highly important, particularly for drugs with low safety margin.

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ANTIBACTERIAL AGENTS IN THE ESSENTIAL DRUGS LIST OF NEPAL

Contributed by **Bimal M. Shrestha**, Pharmacist, Department of Drug Administration, Kathmandu.

HMG/Nepal first published the National Essential Drugs List (EDL) in 1986. The first revision of the list was published in 1992, followed by second revision in 1997. The EDL also consists of separate lists for district, health post, sub-health post and primary care levels.

In the present list of Essential Drugs 1997, the antibacterial agents included are amoxycillin, benzathine penicillin, benzyl penicillin, cloxacillin, procaine benzylpenicillin, chloramphenicol, ciprofloxacin, erythromycin, gentamicin, metronidazole, tetracycline, rifampicin, streptomycin, ethambutol, sulfacetamide, doxycycline, cefotaxime, povidone iodine, mercurochrome, acriflavin, and gentian violet. The following anti-bacterials were present in the 1992 list but were deleted from the 1997 list: ampicillin, neomycin, nalidixic acid, phenoxymethyl-penicillin and trimethoprim.

At different times, the HMG/Nepal has banned various dosage forms and combinations of drugs with antibacterial agents. Such banned formulations and combinations are:

1. Sulphaguanidine and its combination

2. Tetracycline liquid oral preparation
3. Streptomycin in oral dosage form
4. Combination of antibacterial agents with electrolytes
5. Combination of two or more antibacterial agents expect the following:
 - a) combination used for treatment of tuberculosis and leprosy
 - b) combination of two anti-biotics of the penicillin group
6. Combination of vitamin C with tetracycline
7. Combinations of vitamins with anti-tubercular drugs except combination of antitubercular drug isoniazid with vitamin B6

SOURCES

1. National List of Essential Drugs Nepal, Dept. of Drug Administration, HMG/Nepal, 1997 (Second Revision).
2. HMG/Nepal, Nepal Rajpatra Part 3, Khanda 33, No. 11, 2040/3/13 and Nepal Rajpatra Part 3, Khanda 40, No. 31, 2047/8/3

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DRUG PROCUREMENT AT TUTH: PRE-DEFINED CRITERIA FOR TENDER

In 1996, the Tribhuvan University Teaching Hospital (TUTH) Drug Sub-Committee developed the following criteria for procuring drugs by tender and recommended them to the TUTH Administration for implementation. Since that year, these criteria have been implemented by the Hospital.

Parties wishing to bid tender for supplying drugs to TUTH should:

- submit copy of Registration and Renewal with the Department of Drug Administration (DDA).
- submit copy of Good Manufacturing (GMP) Certificate from the concerned drug regulatory authority.
- submit certificate stating that the company's product has been present in the Nepalese market for at least 3 years.
- agree in writing that if tender is won, "batch analysis report" from a Government registered laboratory will be provided.
- agree in writing that TUTH can get "random quality analysis" of the supplied product done in a Government registered laboratory.
- provide written product specification, eg, ingredients, formulation, volume, packing, etc while applying for tender.
- agree in writing to supply drugs with following expiry date from the time of supply:
 - at least 1 year for those with 2 years (or more) expiry period from the date of manufacture.
 - at least 8 months for those with 1 and half years expiry period from the date of manufacture.
 - at least 6 months for those with 1 year expiry period from the date of manufacture.
 - at least 3 months for those with 6 months expiry period from the date of manufacture.