

Review article

Misuses of antibiotics – An overview

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Abstract:

Antibiotics are extremely important tool in modern medicine. The use of antimicrobial agents, especially antibiotics has become a routine practice for the treatment of infective illness. Antibiotic resistance among Pathogenic microorganism is a matter of worldwide concern. Excessive & inappropriate use of antibiotics contributes to development of bacterial resistance. The rising incidence of bacterial resistance to common antibiotics has prompted the need to use the antibiotics judiciously in the practice. Optimal and judicious selection of antimicrobial agents for the therapy of infectious diseases requires clinical judgment and detailed knowledge of pharmacological and microbiological factors.

Keywords: Antibiotic sensitivity test, Antimicrobial agents, Bacterial resistance

Introduction:

Antibiotics are extremely important tool in modern medicine.¹ The use of antimicrobial agents, especially antibiotics has become a routine practice for the treatment of infective illness.^{2,3} Antibiotic resistance among Pathogenic microorganism is a matter of worldwide concern.⁴ Antibiotics are among the most commonly prescribed drugs in hospitals. Excessive & inappropriate use of antibiotics contributes to development of bacterial resistance.⁴ However, there are also reports of an irrational use of antibiotics^{5,6} which may even lead to infections that are worse than the originally diagnosed ones. A vast majority of physicians (97%) believed that widespread and inappropriate use of antimicrobials was an important cause of resistance. However, only 60% favored restricting the use of broad spectrum antibiotics.⁷ Antibiotic agents are selected more likely of habit than for specific indications and dosage.⁸

The rising incidence of bacterial resistance to common antibiotics has prompted the need to use the antibiotics judiciously in the practice.⁹ The main challenges in prescription of antibiotics are to achieve a rational choice and appropriate use of antibiotics and to recognize their potential problems.¹⁰ Information about antibiotic use patterns is necessary for a constructive approach to problems arises from the multiple antibiotics available.¹¹ Optimal and judicious selection of antimicrobial agents for the therapy of infectious diseases requires clinical judgment and detailed knowledge of pharmacological and microbiological factors. Unfortunately, the decision to use antibiotics frequently is made lightly, without regard to the potential infecting microorganism or to the pharmacological features of the drug.¹² However when antibiotic are used to treat an infection, a favorable therapeutic outcome depends upon several factors. For example

Pharmacokinetic factors, pharmacodynamic factors, age of patients etc.⁸

The first decision to be made is whether administration of an antimicrobial agent is truly indicated. Many physicians reflexly associate fever with treatable infections and prescribe antimicrobial agent therapy without further evaluation. This practice is irrational and potentially dangerous; the diagnosis may be masked if appropriate cultures are not obtained prior to the therapy, and antibiotics can cause serious toxicity. Injudicious use of an antimicrobial agent also can result in development of resistance micro-organisms; one does not always have the luxury of a definitive identification of a bacterial infection before treatment must be initiated. In the absence of clear indication, antibiotics often may be used if disease is severe and if it seems likely that withholding therapy will result in failure to manage a potential life-threatening infection.⁸ Whenever the clinician is faced with initiating therapy on a presumptive bacteriological diagnosis, cultures of blood and certain other body fluids should be taken prior to the institution of drug therapy. For definitive therapy the regimen should be changed to a more specific (narrow – spectrum) antimicrobial agent.⁸

Misuses of antibiotics due to-

Antibiotics are frequently misused and overused.⁴

- Treatment of untreatable infections.
- Therapy of fever of undetermined origin.
- Improper Dosage such as, administration of excessive amount, use of suboptimal quantities.¹¹
- Inappropriate reliance on Chemotherapy alone.
- Lack of adequate bacteriological information.

One half of the courses of antimicrobial therapy administered to hospitalized patients appear to be given in the absence of support from microbiological

laboratory. Bacterial cultures and Gram stains of infected material are obtained too infrequently and the results, when available are often disregarded in the selection and application of drug therapy. Frequent use of drug combinations or drugs with the broadest spectra is a cover for diagnostic imprecision. Antimicrobial drug therapy must be individualized on the basis of clinical situation, microbiological information and pharmacological considerations. The recent emergence of antibiotic resistance in bacterial pathogens, both nosocomially and in the community setting is a very serious development that threatens the end of antibiotic era. A more responsible approach to the use of antibiotics, both those that are now available and new agents that might be developed in the future, is essential if the end of the antibiotic era is to be averted.⁸

An antibiotic is a double-edged sword. Used judiciously it can do good and used recklessly it can be harmful. Unfortunately, because of erratic use of antibiotics many organisms have emerged in the human environments who have acquired resistance to many antibiotics. Initially when the antibiotics discovered rapidly, microbes lagged behind in acquiring resistance. But now picture is reversed. The space of microbes acquiring resistance is more than the speed with which new antibiotics are being discovered. Some bacteria evolved to the extent that they have become “superbugs.”¹ Researcher is hard working for developing new antibiotics. But unless we stop the rampant misuse of antibiotics, the effectiveness of new drugs will continue to be compromised. The study of prescribing patterns seeks to monitor, evaluate and suggest⁴ modification in practitioners prescribing habits so as to set more rational attitude toward antibiotic use.¹ Several professional societies have issued guidelines

designed to reduce the use of antibiotics world-wide by means of various strategies.^{9,12}

Quality of life can be improved by enhancing the standard of medical treatment at all levels of health care delivery system.^{13,14} “Survival of the fittest” holds good for men and animals as also for bacteria. A majority of bacteria in nature are nonpathogenic, a large number of them, live as commensals on our body leading a symbiotic existence. A limited population of bacteria which has become pathogenic was also sensitive to antibiotics to begin with. It is the man made antibiotic pressure, which has led to the emergence and spread of resistant genes amongst bacteria. Despite the availability of a large arsenal of antibiotics, the ability of bacteria to become resistant to antibacterial agents is amazing. This is more evident in the hospital settings where the antibiotic usages are more.

The use of antibiotics is widespread in clinical medicine, agriculture, aquaculture, veterinary practice, and poultry and even in household products. The major reason for this is the inappropriate use of antibiotics due to a lack of uniform policy and disregard to hospital infection control practices. The antibiotic cover provided by newer antibiotics has been an important factor responsible for the emergence of multi-drug resistant bacteria. Bacterial infections increase the morbidity and mortality, and prolong hospital stay adding to the economical burden on the patient. The problem is further compounded by the lack of education and “over the counter” availability of antibiotics in developing countries.

Antibiotic resistance is now all pervasive with the developed world as much vulnerable to the problem. Despite advancement in medical technology for diagnosis and patient care, a person can still die of an

infection caused by multi-drug resistant bacteria. It is time to think, plan and formulate a strong antibiotic policy to address the burgeoning hospital infection.¹⁵ More than 90 percent of the deaths from infectious diseases worldwide are caused by only a handful of infectious diseases. These diseases - lower respiratory infections, HIV/AIDS, diarrheal diseases, tuberculosis, malaria and measles. And, while not major killers, a number of the world's 'neglected' infectious diseases such as lymphatic filariasis, trachoma, intestinal parasites, leprosy and onchocerciasis cause chronic disability and stigma for millions. Illness and death from infectious diseases are particularly tragic because they are largely preventable and treatable. 10 percent of world's population accounted for more than 40 percent of deaths due to infectious diseases.¹⁶

Antibiotics resistance has become a serious public health concern with economic and social implications throughout the world, be it community acquired infections like Streptococcal infections, pneumonia, typhoid fever, *etc.*, or hospital acquired infections due to methicillin resistant *Staphylococcus aureus* (MRSA), vancomycin resistant enterococci (VRE), vancomycin intermediate *S. aureus* (VISA) or extended spectrum beta-lactamase (ESBL) enzyme producing Gram negative bacteria. These infections lead to higher rates of hospitalization, longer hospital stay, and increase in the cost of treatment and thus increased economic burden on the community.¹⁷

Certain bacteria have a propensity to cause infection in particular common body sites or fluids. Antibiotic may be chosen before results of the culture are available based on some preliminary information, such as¹⁸

-Site of infection and likely causative organism

-Gram-stain result (does result correlate with potential organism above)

Ideally, before beginning antibiotic therapy, the suspected areas of infection should be cultured to identify the causative organism and potential antibiotic susceptibilities.

Selection of an antimicrobial agent⁸

In most situations, identification of the morphology of the infecting organisms is not adequate to arrive at a specific bacteriological diagnosis and the selection of a single narrow –spectrum antibiotic may be inappropriate particularly if the infection is life threatening. Broad antimicrobial coverage is then indicated, pending isolation and identification of the microorganism. Many factors need to be considered before this change is made.

Testing for microbial sensitivity to antimicrobial agents -

There may be wide variations in susceptibility of different strains of the same bacterial species to antibiotics. Essential to the choice of drug is information about the pattern of sensitivity of the infecting microorganism. Several tests are now available for determination of bacterial sensitivity to antimicrobial agents.

The two tests that are most commonly used are Disk diffusion and Agar or Broth dilution tests.

The disk diffusion technique is simple to perform and relatively inexpensive. It provides only quantitative or semi quantitative information on the susceptibility of a given microorganism to given antibiotic. The test is performed by applying commercially available filter- paper disks impregnated with specific quantities of the drug onto the surface of agar plates over which a culture of the microorganism has been streaked. After 18 to 24 hours of incubation, the size of a clear zone of inhibition around the disk is

determined; this is related to the activity of the drug against the test strain standards for sensitivity vary for each microorganism , and they are based on the concentration of drug that can be achieved safely in plasma without producing toxicity.

Even though the concentration of the antibiotic in plasma is the standard used for these tests, it may not always reflect the drug concentration at the site of the infection. There are several notable exceptions, where the disk diffusion test may not accurately predict therapeutic effectiveness Methicillin-resistant staph. aureus, which may appear to be sensitive to cephalosporins and trimethoprim- sulfamethoxazole; and Shigella species, which may appear to be sensitive to cephalosporins. These drugs have been proven not to be useful in such infection.

Dilution test employ antibiotics in serially diluted concentrations in solid agar or broth media containing a culture of the test microorganism. The lowest concentration of the agents that prevents visible growth after 18 to 24 hours of incubation is known as the minimal inhibitory concentration (MIC) and the lowest concentration that results in a 99.9% decline in bacterial numbers is known as the minimal bactericidal concentration (MBC).

Pharmacokinetic factors-

It should be the aim of antimicrobial therapy to produce antibacterial concentrations of drug at the site of infection during the dosing interval. This can be achieved only if the pharmacokinetic and pharmacodynamic principles are understood and employed.

The activity of β – lactam antibiotics, for example, is primarily time dependent whereas that of aminoglycosides is concentration dependent. Activity may also depend upon the specific organism and the site of infection. Studies in animals with meningitis

suggests that pulse dosing (Intermittent administration) of β – lactam antibiotics may be more efficient, it appears that constant activity is superior in other experimental infections. Experimental data suggests that aminoglycosides are at least as efficacious, and are less toxic when given in single, large daily dose as when given more frequently.

Route of administration-

Oral route of administration is preferred whenever possible, parenteral administration of antibiotics usually is recommended in seriously ill patients in whom predictable concentrations of drug must be achieved.

Host factors-

Innate host factors are prime determinants for drug selection and also for dosage, route of administration.

Host defense mechanism-

A critical determinant of therapeutic effectiveness of antimicrobial agents is the functional state of host defense mechanisms.

Both humoral and cellular immunity are important. Inadequacy of type, quality and quantity of immunoglobulin, may result in therapeutic failure despite the use of otherwise appropriate and effective drugs for example, most of AIDS patients with bacteremia due to salmonella will respond to conventional therapy but this infection will relapse even after prolonged treatment.

Local factors-

Local factors at the site of infection affect the antimicrobial activity of the drug.

Pus, which consists of phagocytes, cellular debris; fibrins, and protein, binds aminoglycosides and vancomycin, resulting in a reduction in their antimicrobial activity.

The PH in abscess cavities and in other confined sites (pleural space, CSF, and urine is usually low,

resulting in a marked loss of antimicrobial activity of aminoglycosides, erythromycin and clindamycin.) Aerobic or anaerobic condition at the site of infection. Presence of foreign body in infected site.

Age-

The age of the patient is an important determinant of pharmacokinetic properties of antimicrobial agents. Mechanisms of elimination, especially renal excretion and hepatic biotransformation are poorly developed in the newborn especially premature infant. Failure to make adjustments for such differences can have disastrous consequences. (Gray baby Syndrome caused by chloramphenicol). Elderly patients also may have significantly reduced rates of creatinine clearance and drug metabolism. Also, elderly patients are particularly susceptible to ototoxic effect of aminoglycosides.

Genetic factors-

Certain genetic or metabolic abnormalities must be considered when prescribing antibiotics. A number of drugs including the sulfonamides nitrofurantoin, chloramphenicol and nalidixic acid may produce acute hemolysis in patients with glucose -6-phosphate dehydrogenase deficiency.

Pregnancy-

Pregnancy imposes an increased risk of reaction to some antimicrobial agents for both mother and fetus.

Drug allergy-

Antibiotics are notorious for provoking allergic reactions.

Therapy with combined antimicrobial agents⁸

The simultaneous use of two or more antimicrobial agents has a certain rationale and is recommended in specifically defined situations. However, selection of an appropriate combination requires an understanding of the potential for interaction between the antimicrobial agents. Such interactions may have

consequences for both the microorganism and the host. Since the various classes of antimicrobial agents exert different actions on microorganism, one drug has the potential to either enhance or inhibit the effect of the second. Similarly combinations of drugs that rationally might be used to cure the infections may have additive or supraditive toxicities. For example, Vancomycin when given alone usually has minimal nephrotoxicity; as does tobramycin, however when the drugs are given in combination they cause marked impairment of renal function.

Indications for the clinical use of combinations of antimicrobial agents:-

1. Treatment of mixed Bacterial infections
2. Therapy of severe infections in which a specific cause is unknown.
3. Enhancement of antibacterial activity in the treatment of specific infection.
4. Prevention of the Emergence of resistant microorganism.

Failure of antibiotics therapy⁸

Antibiotics are frequently misused and overused that may lead to antibiotic treatment failure¹⁶

Treatment of untreatable infections-

A common misuse of antibiotics is in infections those have been proved by experimental and clinical observation to be untreatable. The majority of the diseases caused by viruses are self limited and do not respond to any of currently available anti-infective compounds. Thus antimicrobial therapy of measles, mumps and at least 90% of infections of the upper respiratory tract is ineffective and therefore useless.

Therapy of fever of undetermined origin-

Most instances of pyrexia of a short duration in the absence of localizing signs are probably associated with undefined virus infection and do not respond to antibiotics.

Improper dosage-

Erroneous dosages of antibiotics are of 2 types.

- Administration of excessive amount
- Use of suboptimal quantities

Drugs such as amino glycosides frequently are administered at sub therapeutic doses, probably because of fear of toxicity; the potential for clinical failures and selection of resistant organisms is thus increased.

Inappropriate reliance on chemotherapy alone-

As a general rule, when an appreciable quantity of pus, necrotic tissue or a foreign body is present, the most effective treatment is a combination of an antimicrobial agent given in adequate dose plus properly performed surgical procedure.

Lack of adequate bacteriological information-

One half of the courses of antimicrobial therapy administered to hospitalized patients appear to be given in the absence of support from microbiological laboratory. Bacterial cultures and Gram stains of infected material are obtained too infrequently and the results, when available are often disregarded in the selection and application of drug therapy. Frequent use of drug combinations or drugs with the broadest spectra is a cover for diagnostic imprecision.

Conclusion:

Antibiotics are used in two general ways -as empirical therapy and as definitive therapy. When used as empirical therapy, or initial, therapy, the antibiotic must "Cover" all of the likely pathogens, since the infecting organism(s) has not yet been defined. Combination therapy or treatment with a single broad-spectrum agent often is employed. However, once the infecting microorganism is identified, definitive antimicrobial therapy should be instituted – a narrow spectrum, low – toxicity regimen to complete the course of treatment.

Antimicrobial drug therapy must be individualized on the basis of clinical situation, microbiological information and pharmacological considerations.

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