Antibiotics are critical in the treatment of bacterial infections. The discovery of penicillin was followed by an extraordinary progress in research related to antibiotics and their extensive use. Drastic improvement in mortality and morbidity due to infectious diseases during 1980s led to great euphoria and complacence amongst medical fraternity. The result of this was misuse or inappropriate use of antibiotics with emphasis of curative medicine at the cost of disease preventive measures. Excessive use of antibiotics resulted in the emergence of bacterial resistance\(^1\). The resistant strains had a survival advantage, and under the selective pressure of antibiotics propagated and spread throughout the world.

The challenge of antibiotic resistance: Need to contemplate

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“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 became 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 usage is maximum. The use of antibiotics is widespread in clinical medicine, agriculture, aquaculture, veterinary practice, 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, increase the cost of treatment, and prolong hospital stay adding to the economical burden on the nation. 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 a multi-drug resistant bacteria. It is time to think, plan and formulate a strong antibiotic policy to address the burgeoning hospital infection.

**Key words** Antibiotic - control of resistance - emerging antibiotic resistance - multidrug resistance - resistance

Antibiotics are critical in the treatment of bacterial infections. The discovery of penicillin was followed by an extraordinary progress in research related to antibiotics and their extensive use. Drastic improvement in mortality and morbidity due to infectious diseases during 1980s led to great euphoria and complacence amongst medical fraternity. The result of this was misuse or inappropriate use of antibiotics.
Antibiotic resistance, a well known phenomenon in nature\(^2\) assumes significant public health importance when it gets amplified many folds due to human misuse and neglect. In the present age the threat has become global due to rapid spread of organisms from one part of the world to another. It is no longer a problem of the developing countries alone. Today even after all the advances in therapeutics and the availability of a large number of antibiotics, a person can die in a developed country also due to infection with resistant bacteria\(^3\).

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\(^4\). The problem is much larger in developing countries\(^5\). The economic consequences have greater implications on the already overburdened economy of these countries. There are many factors that could be responsible for the increase in antibiotics resistance in developing countries\(^6\). The combination of a heavy disease burden, huge populations, rapid spread through crowding, poor sanitation and inappropriate use of the available drugs all contribute to this problem. This is further complicated by the availability of antibiotics in open markets without proper prescriptions in majority of these countries. Many a time, the amount of antibiotics given is inadequate to treat serious infections due to poverty or lack of education. Infectious diseases, and therefore antibiotic resistance also thrive in conditions of civil unrest, mass migration and unhygienic environmental conditions where large numbers of people are exposed to infectious diseases with little health care infrastructure\(^6\).

The situations where overuse or abuse of antibiotics is common in clinical practice are many, for example, treatment of non bacterial diseases or of self limiting bacterial diseases; inappropriate antibiotic prophylaxis; errors in generic choice, route, dosing and duration of therapy or inappropriate combination therapy\(^7\). There are various reasons which influence this decision like feeling of insecurity; patients’ expectations; aggressive marketing by pharmaceutical companies; lack of uniformity among physicians to follow antibiotic policy; impact of recent clinical trials and at times lack of knowledge of the microbiological aspects of infectious diseases or the pharmacokinetics of the drug\(^7\).

For sometime, progress in the development of newer and effective antibiotics kept pace with the emerging antibiotic resistance. But the present scenario is such that the available antibiotics have become ineffective in diseases of proven bacterial etiology especially in a hospital setting.

**Mechanism of resistance**

The use of antibiotics should have created a catastrophic situation for microbial populations but the genetic flexibility allowed bacteria to survive and multiply under the antibiotic pressure.

Bacteria can resist antibiotics as a result of chromosomal mutation or by exchange of genetic materials, which carry resistance genes, through transformation, transduction or conjugation by plasmids\(^8\). The mechanism of resistance to antimicrobial agents can be due to\(^9\)

(i) Impermeability of the drug: This is the most frequent cause of intrinsic resistance. Resistance in *Enterococcus sp.* and *Pseudomonas aeruginosa* is a good example of such mechanisms; (ii) alteration in target molecules—This is one of the most important mechanisms of resistance to clinically used antibacterial drugs, for example, methicillin resistant *S. aureus* with altered penicillin binding proteins; (iii) enzymatic drug modifications—\(\beta\)-lactamase enzymes currently account for most of the resistance to penicillins and cephalosporins. \(\beta\)-lactamas affect a common drug site i.e., \(\beta\)-lactam ring. Penicillins, cephalosporins, monobactams and carbapenems can all be hydrolyzed by multiple members of the beta
lactam family of enzymes, resulting in a microbiologically ineffective compound. The other important class of antibiotics, which are destroyed by enzymes are aminoglycosides due to the action of aminoglycoside-modifying enzymes produced by the bacteria; (iv) efflux—The role of efflux of drug from the bacterial cell as a resistance mechanism is comparatively less common in clinical practice.

Although both chromosomal mutations or genetic transfer can be responsible for the resistance acquisition, it is the transferable resistance which poses a great threat as it can achieve much larger dimensions due to wide and rapid dissemination. This transferable resistance is carried on R plasmids. A single plasmid can carry a number of genes coding for multiple drug resistance. It has been suggested earlier that evolution of multi-drug resistant plasmids in pathogens is a comparatively recent phenomenon which came into existence after the introduction of antibiotics after 1940s. This further supports the observation that the use of antibiotic itself has been responsible for emergence of resistance in the pathogenic bacteria in clinical practice.

While plasmids act as vectors of resistance genes, the genes themselves are most often located on discrete movable DNA elements called transposons. The important process in the gene pick up is done by transposons carrying multiple antibiotic resistance genes. Integron is the key structural constituent of a transposons. Integron is a mobile DNA element with a specific structure consisting of two conserved segments flanking a central region - "cassette". Genes encoding functions like resistance can be inserted in this region. These transposes carrying (R) genes have the ability to enter a conjugative plasmid or a chromosomes.

Evolution of resistance

The origin of resistant genes could be due a natural process whereby the resistant genes are maintained in nature because of the presence of antibiotics producing bacteria in soil. These antibiotics act on other bacterial species other than the producer bacteria. There has to be a mechanism of protection in the host bacteria against the antibiotics that it produces, which could be the source of genes encoding resistance. Resistance to penicillin in S. aureus was observed just a few years after penicillin came into use.

As the next generations of antibiotics were developed to overcome the problems of resistance against available antibiotics, bacteria developed mechanisms to resist the newer antimicrobial also. For example, the resistance to penicillin initially was due to production of an enzyme penicillinase by bacteria, antibiotics like cloxallin were developed which was resistant to penicillinase enzyme. To resist these antibiotics bacteria altered the target site for binding of β-lactam antibiotics i.e., PBPs and this led to the development of MRSA. Simultaneously attempts were being made to develop newer generations of cephalosporins with wide range of activity and resistance to existing known β-lactamase enzymes. The 3rd and 4th generations of cephalosporins were introduced which were not destroyed by the β-lactamases produced by the Gram negative bacteria. However, after the wide use, the bacteria responded by developing mechanisms producing ESBL to destroy these drugs. To overcome this problem carbapenems were introduced, which were resistant to ESBL enzymes. These agents were the best in the β-lactam group of antibiotics but no sooner have they came into use, the bacterial populations started producing carbapenemases which hydrolyze carbapenems.

Thus it is evident that though numerous β-lactam antibiotics have been developed during the last 40 yr in an attempt to circumvent the activity of β-lactamases, the prime result of this has been the selection of more diverse and potentially more deleterious enzymes hydrolyzing all β-lactams. The situation is alarming because β-lactams are otherwise the best bactericidal agents which when combined with aminoglycosides another bactericidal agent, make a synergistic combination and is an ideal choice for all types of critical infections. This is also the best choice of empirical therapy in infections in an immunocompromised host and in patients in high risk units.
Another classical example of emergence of resistance due to abuse of antibiotics is the extensive use of vancomycin. As the infections due to MRSA in hospitals all over the world increased, vancomycin became the drug of choice to treat these infections. This led to the selection of VRE present as normal flora in the gut of the patient, and possibly contributed to the emergence of VRE besides other factors.

Various contributing factors responsible for emergence of antibiotic resistance are:

(i) Lack of education—The combination of poverty and ignorance makes the ground perfect for resistance development. Important reason for irrational therapy is inability to buy adequate quantity of antibiotics or to reach qualified doctors due to poverty or ignorance for rational prescriptions of antibiotics.

(ii) Hospital acquired infections—Hospitals are the places where the selective pressure of antibiotics is the highest as the hospital bacteria are mostly multi drug resistant. The main reason for this is the increase in hospital associated infections because of the disregard to standard isolation precautions in most of the busy hospitals with limited resources.

(iii) Use of antibiotics in agriculture or aquaculture—Antibiotics are used widely in agriculture and aquaculture for therapeutic, prophylactic and growth promoting purposes. The presence of residual antibiotics in the flesh of animals may result in direct exposure of the consumers to these drugs. In addition, the presence of low levels of antibiotics may select for resistant bacteria in the intestines of animals intended for human consumption. The animals can be contaminated with facial bacteria during the slaughter process and therefore contaminate the meat reaching the consumer. Emergence of VRE is one particular example of appearance of resistant bacteria in animals that have affected susceptible human populations. Antibiotics resistant bacteria can also be found on fruits and vegetables due to spreading of sewage sludge on farm land or use of antibiotics directly on fruit and vegetable crops.

(iv) Environmental factors—The presence of antibiotic resistant bacteria in fresh water sources has been documented from different parts of the world. Selection of resistant organism in nature may result from the natural production of antibiotics by soil organisms, or contamination from animal feed or crops or waste products from treated animals or humans. Resistant organisms from farming practices may be transferred into rivers and other water sources through waste disposal system or by drainage or rain water from farm land. All these factors contribute to the natural reservoirs of resistance genes which may provide a source of transferable genes.

(v) Use in household products—There is an increase in the use of surface antibacterial agents over the years into healthy households. The antibacterial substances added to diverse household cleaning products are similar to antibiotics in many ways. These products can also select out resistant strains.

Resistant microorganisms

Salmonella typhi and S. paratyphi A

Enteric fever continues to be a major public health problem in our country. Chloramphenicol remained the drug of choice for the treatment of this infection till plasmid mediated chloramphenicol resistance was encountered.

Following this ciprofloxacin became the mainstay of treatment. Being a safer and more effective drug it was used even when the bacteria was sensitive to chloramphenicol. The isolates of S. typhi and S. paratyphi A showed higher MIC to ciprofloxacin and there is clinical resistance to treatment with ciprofloxacin in the patients suffering from enteric fever. The choice left now is an expensive drug like ceftriaxone or cefexime.

Infections with S. paratyphi A, which were always considered to be mild have also shown similar trends and the complications occur if the treatment is delayed.

Shigella sp.

The emergence of multi drug resistant Shigella has remained a cause of concern in endemic regions. The nalidixic acid resistance has increased for
Shigella sonnei in some of the Indian isolates. This is noteworthy, since it has been recommended for the empirical treatment of patients suspected to have shigellosis. Multi drug resistant Shigella dysenteriae serotype 1 strains have re-emerged in patients hospitalized with diarrhoea which were multi drug resistant (resistant to norfloxacin and ciprofloxacin).

Vibrio cholerae

Resistance in V. cholerae is being encountered in most of the endemic areas. Overall 90 per cent of V. cholerae isolates show resistance to at least one of the commonly used antibiotics to treat gastrointestinal infections. The resistance to nalidixic acid being the highest followed by furazolidine, co-trimoxazole and tetracycline. Though the role of antibiotics is limited in the management of cholera, they still play an important role in the management of critically ill patients who need hospitalization.

Methicillin resistant Staphylococcus aureus (MRSA)

MRSA is an important cause of nosocomial infections worldwide. These are also resistant to most of the other antibiotics and in many cases the only choice left is vancomycin. There is evidence to show that MRSA is not only limited to hospital environment but can cause infections in community, a fact which is alarming. This could be due to the carriers in the hospitals being discharged or health care workers carrying it with them. Similarly methicillin resistant coagulase negative staphylococci (CoNS) are also increasing in numbers in such environment, and the multi drug resistant strains are higher amongst CoNS. As yet no vancomycin or teicoplanin resistance has been reported from India. But continuous monitoring is required as presence of VISA strains has been reported causing infections in some parts of the world.

Enterococcus sp.

The enterococci are inherently resistant to many antibiotics but the combination of penicillin and gentamicin being synergistic remained the treatment of choice for infections related to this bacteria. Now the strains have emerged which do not respond to treatment with this combination as they have a high level of resistance of aminoglycosides and are called as HLAR. Vancomycin is the only alternative left for the treatment of infections caused by HLAR strains. But a major problem is that vancomycin use is a risk factor for colonization and infection with VRE. Vancomycin resistance, emerging amidst the increasing incidence of high level resistance to penicillins and aminoglycosides, has limited treatment options for bacteraemia due to E. faecalis or E. faecium in the hospitals, which is increasingly being encountered. Though at present there is limited number of reports of VRE from India, it needs continuous monitoring. All these strains are presently sensitive to linezolid.

Emergence of VRE may also increase the possibility of the emergence of vancomycin resistant St. aureus. Conjugative transfer of high level vancomycin resistance from E. faecalis to S. aureus in the laboratory has been possible and there is a possibility that this resistance may be transferred to wild type S. aureus.

Streptococcus pyogenes

S. pyogenes, the group A streptococcus has remained sensitive to penicillin till now but it continues to cause invasive infections and toxic shock syndrome. Indian isolates have remained sensitive to penicillin but the resistance to macrolide is being encountered. The penicillin susceptibility of this organism now needs continuous monitoring.

Streptococcus pneumoniae

There is a concern of spread of penicillin resistant S. pneumoniae strain throughout the world. Though the prevalence of this resistance is at present not a major problem in our country, intermediate resistance to penicillin has been reported. Resistance to co-trimoxazole and chloramphenicol is seen more frequently. The isolates showing total resistance to penicillin have been reported from India, which were also multi drug resistant being resistant to cefotaxime, erythromycin, chloramphenicol and trimethoprim sulphamethoxazole.
**Haemophilus influenzae**

In India, β-lactamase mediated resistance in *H. influenzae* is increasingly being encountered. Recently a multicentric study showed an increasing resistance to ampicillin, chloramphenicol, erythromycin and trimethoprim-sulphamethoxazole in *H. influenzae* strains isolated from different parts of India. All the strains however were sensitive to cefotaxime.

**Gram negative bacilli**

The most important cause of hospital acquired infections are the Gram negative bacteria. These bacteria have acquired resistance to multiple antibiotics. Not only in the hospital settings but also in the community acquired infections the Gram negative bacteria pose therapeutic problem. *E. coli* is an important cause of community acquired urinary tract infections but resistance is seen in nearly 70-80 per cent of the strains to the commonly used antibiotics. In patients suffering from cystic fibrosis colonization with *Psuedomonas aeruginosa* in the community set up is very common. These patients can harbour multi drug resistant strains over a period of time as they are on long term antibiotic prophylaxis and need frequent antibiotic treatment.

Among the nosocomial pathogens multi drug resistant Gram negative bacteria are the important cause of hospital associated infections. These bacteria can survive for a long period of time in adverse environment and once having entered the host, can lead to long term colonization. Nosocomial infections due to ESBL producing *Klebsiella pneumoniae*, *P. aeruginosa*, *Acinetobacter baumanii*, *Serratia marsecens*, *E. coli* etc., are the main threat in the present scenario. The therapeutic options are limited in infections caused by these agents.

**Control**

If an infection is addressed in a comprehensive and timely manner, resistance can be contained. Appropriate use of antibiotics will delay and in many cases prevent the emergence of resistance. Historically, several approaches to antibiotic prescribing have been employed to address antimicrobial resistance. One approach is to use a newer more potent antimicrobial in settings where resistance has emerged to an older agent. However, if newer agents are overused or used inappropriately, resistance will invariably develop to the newer drug. Another approach to combating resistance is to continue using older agents as first line choices, in preference to newer, more potent drugs, in an effort to preserve the activity of the new drugs. Thus the newer agents are reserved for infections caused by mutated multiresistant strains. However, as resistance continues to increase to the first line agents, poor outcomes and secondary costs associated with clinical failures increase. Efforts to overcome bacterial resistance range from judicious and rationale use of antibiotics, effective hospital infection control programme and research in the field related to development of newer antibiotics. The use of antibiotics in the community can be restricted by implementing laws to stop over the counter sale of antibiotics. Another approach is to use a combination therapy.

The most recent interest has been in rotating use of antibiotics. Some studies have suggested the usefulness of this strategy but this has to be done with close microbiological monitoring. Appropriate antimicrobial use is an integral component of any programme to slow the emergence and spread of antimicrobial resistant microorganisms in the health care setting. Though many possible interventions have been proposed, deciding which one is the most effective in a particular setting can be difficult. Despite guidelines from governmental and professional groups, many hospitals have yet to institute any antimicrobial use policies or programmes to improve antimicrobial agent prescribing.

Limiting the spread of antibiotic resistant bacteria in hospitals now invesages restrained and limited use of antimicrobial agents and improve hospital hygiene - both easier to state than to implement. Hospital infection control will prevent the spread of infection and colonization of patients especially in high risk areas with multi drug resistant strains of bacteria. This will minimize the use of antibiotics in hospitals. More importantly, rationale policies are urgently needed to promote rational use of antibiotics in poultry, animal husbandry and agriculture.
References


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