

ANTIBIOTIC RESISTANCE –A GLOBAL ISSUE OF CONCERN

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Antibiotic resistance is currently the greatest challenge to the effective treatment of infections globally. Resistance adversely affects both clinical and financial therapeutic outcomes, with effects ranging from the failure of an individual patient to respond to therapy and the need for expensive and/or toxic alternative drugs to the social cost of higher morbidity and mortality rates, longer duration of hospitalization, and the need for changes in empirical therapy. Thus the astonishing effects of antibiotics, the occurrence of resistance and the considerable resources spent on antibiotics globally are convincing reasons for concern about ensuring adequate and proper use of these powerful agents.

Keywords : Antibiotic, Microbial resistance, Microbes, Infection.

INTRODUCTION

Antibiotic resistance occurs when bacteria change in some way that reduces or eliminates the effectiveness of drugs, chemicals or other agents designed to cure or prevent the infection. Thus the bacteria survive and continue to multiply causing more harm. Widespread use of antibiotics promotes the spread of antibiotic resistance. Bacterial susceptibility to antibacterial agents is achieved by determining the minimum inhibitory concentration that inhibits the growth of bacteria.¹

Resistance is defined as bacteria that are not inhibited by usually achievable systemic concentration of an agent with normal dosage schedule and/ or fall in the minimum inhibitory concentration ranges. Likewise the multiple drug resistance is defined as the resistance to two or more drugs or drug classes.² Acquisition of resistance to one antibiotic conferring resistance to another antibiotic, to which the organism has not been exposed, is called cross resistance.³

Antibiotics are given to human for treatment and prophylaxis of infectious diseases, 80% to 90% of antibiotics are used in outpatients and the remainder in hospitals. Antibiotics appear to be used not only in excess but also inappropriately and this accounts for 20% to 50 % of all antibiotics used.^{4,5} The Center for Disease Control and Prevention in USA has estimated that some 50 millions of the 150 millions prescriptions every year are unnecessary.⁶

Nowadays, about 70 % of the bacteria that cause infections in hospitals are resistant to at least one of the antibiotic agents most commonly used for treatment. Some organisms are resistant to all approved antibiotics and can only be treated with experimental and potentially toxic drugs. An alarming increase in resistance of bacteria that cause community acquired infections has also been

documented, especially the Staphylococci and Pneumococci (*Streptococcus pneumoniae*), which are prevalent causes of disease and mortality. In a recent study, 25% of bacterial pneumonia cases were shown to be resistant to Penicillin, and an additional 25% of cases were resistant to more than one antibiotic.⁷

Antibiotic usage resistance rates vary from one country to another.^{8,9} It is observed that countries with the highest per capita antibiotic consumption have the highest resistance rates. It is not only the amount of antibiotic used that select for resistance, but the number of individuals receiving the drug and the population density also matters.⁴ Giving 1000 doses of an antibiotic to one individual will have considerably less ecological effect on resistance emergence than giving those same 1000 doses to 1000 individuals.¹⁰ A study by Levy suggests that combination of antibiotic use and population density correlates more strongly with the prevalence of antibiotic resistance in a population than use of the antibiotic alone.¹¹

History

The first antibiotic, Penicillin (discovered in 1929 by Sir Alexander Fleming), had unbelievable ability to treat the bacterial infections especially those caused by *Staphylococcus* and *Streptococci* without harming the host.¹² Antibiotic resistance first became challenging shortly after Penicillin gained extensive use in the 1940s.¹³ Nowadays more than 95% of *Staphylococcus aureus* isolates globally are resistant to Penicillins.¹⁴ An initial response to Penicillin resistance was the development of Methicillin, a semisynthetic penicillin.¹⁵⁻¹⁶ The period of late 1940s and early 1950s saw the discovery and introduction of broad spectrum antibiotics such as Streptomycin, Chloramphenicol and Tetracycline and the age of antibiotic chemotherapy came into full being. These antibiotics were effective against the full array of bacterial pathogens including Gram- positive

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and Gram- negative bacteria, intracellular parasites and the *Tuberculosis bacillus*. Synthetic antimicrobial agents such as the “sulfa drugs” (Sulfonamides) and anti-tuberculosis drugs, such as Para-aminosalicylic acid (PAS) and Isoniazid (INH), were also brought into wider usage. However, by 1953 during Shigella outbreaks in Japan, strain of the Dysentery bacillus was isolated which was multiple drug resistant, exhibiting resistance to Chloramphenicol, Tetracycline, Streptomycin and Sulfanilamide.¹² By the late 1980s even Methicillin-resistant *Staphylococcus aureus* had become prevalent in many hospitals and difficult to treat.¹⁵⁻¹⁶ Until recently Vanomycin was a dependable drug for the treatment of infections caused by multidrug resistant Enterococci but Vanomycin resistance began to emerge in the mid 80s. A study by Gaynes reported that Vanomycin resistance had increased more than 20 fold from 1989 to 1995.¹⁷ An additional community acquired pathogen *Neisseria Gonorrhoeae* has undergone significant changes in antibiotic resistance. For a number of years, Penicillins were the drug of choice to treat Gonorrhoeae but in 1976, the plasmid mediated Beta lactamase of *E.coli* was found in *Neisseria Gonorrhoeae* isolates in Africa and Asia.¹⁸

Development of antibiotic resistance was first reported in animal models in 1940s¹⁹ and subjectively reported among patients in the 1970s.²⁰ Today drug resistant strains of *Mycobacterium tuberculosis* are threatening to outbreak in one of the world's most prevalent infectious diseases.¹

Consequences

The antibiotic resistance to microbes leads to severe consequences. Infections caused by resistant microbes fail to respond to treatment resulting in prolonged illness and greater risk of death, longer periods of hospitalization and infections which increases the number of infected people moving in the community. When an infection becomes resistant to first line antibiotic, treatment has to be switched to second or third line drugs, which are always much more expensive and sometime more toxic as well.²¹ In poor countries, where many of the second or third line therapies for drug resistant infections are not available, making the potential of resistance to first line antibiotics considerably greater. The limited number of antibiotics in these countries are becoming increasingly inadequate for treating infections and necessary antibiotics to deal with infections caused by resistant pathogens are absent from essential drug list.²²

Causes

The driving force of antibiotic resistance is the widespread use of antibacterial drugs. More than half of patients in

acute care hospitals receive antibiotics as treatment or prophylaxis.²³ Approximately 80% of antibiotics consumption takes place in the community for human use and atleast half of this considered are based on incorrect indication, mostly viral infection.²¹ Hospital physicians often prescribe antibiotics excessively and inappropriately. There are various factors that contribute to the occurrence of resistance such as; incorrect use of antibiotics, patient related factors, prescriber's prescriptions, use of monotherapy, hospitals, veterinary prescriptions, commercial promotion, over the counter sale of antibiotics, under use of microbiological testing and globalization.²

Incorrect use of antibiotics such as too short a time, at too low a dose, at inadequate potency or for the wrong diagnosis always enhances the likelihood of bacterial resistance to these drugs. Patient related factors are major drivers of inappropriate use of antimicrobials. Many patients believe that new and expensive medications are more efficacious than older agents. This perception increases the unnecessary health care expenditure and encourages the selection of resistance to these newer agents as well as to older agents in their class.²¹ Patient's misperception about the utility of antibiotics in self resolving viral infections, poor compliance where patient forgets to take medication or interruption of treatment when they begin to feel better or may be unable to afford the treatment, self medication which may be unnecessary or often inadequately dosed, are major factors contributing to resistance.^{2,21} Lack of knowledge amongst patients and past experience contributes to increased demand for antibiotics.²⁴ Whether genuine or professed, patient's expectation for antibiotics have an effect on physician's prescribing behaviour.²⁵ Prescribing just to be on the safer side increases, when there is diagnostic uncertainty, lack of prescriber's knowledge regarding optimal diagnostic approaches or lack of opportunity for patient follow up.²¹ Insufficient training in infectious diseases and antibiotic treatment, difficulty of selecting the appropriate anti-infective drugs empirically and need for self reassurance are promoting the use of broad spectrum drugs.²³ Likewise, compliance of healthcare staff with basic infection control practices, such as hand washing or disinfection, is incomplete, and shortage of healthcare staff often makes isolation precautions difficult to implement.²⁶ Use of monotherapy as opposed to combination therapy favors selection of resistance in certain infections.^{16,27-28} Epidemic and endemic infections caused by multiple resistant strains followed intense antibiotic use in many hospitals, particularly in intensive care unit which is the major breeding ground for antibiotic resistance.^{2, 29-31} The

combination of highly susceptible patients, intensive and prolonged antibiotic use and cross infection has resulted in development of nosocomial infections with highly resistant bacterial pathogens. Resistant hospital acquired infections are expensive to control and extremely difficult to eradicate.²¹

Following their success in medicines for human beings, antibiotics have been increasingly used to treat and prevent diseases in animals and plants. The largest quantities are used as regular supplements for prophylaxis or growth promotion, thus exposing a large number of animals, irrespective of their health status to increasingly sub-therapeutic concentration of antibiotics and increasing the occurrence of resistance to these life saving drugs.²¹ Another predisposing factors related to the modalities of treatment are; commercial promotion by the pharmaceutical companies, over the counter sale of antibiotics, under use of microbiological testing, and globalization, which stimulates the international circulation of goods and people and plays an important role in dissemination of pathogens including resistant strains.²

Impact of resistance on public health and economy

Due to the selection pressure caused by antibiotic use, a large pool of resistant genes has been created³² and this antibiotic resistance places an increased burden on society in terms of high morbidity, mortality and cost.² Patient infected with drug resistant organisms are more likely to have ineffective therapy, longer duration of hospital stay, need of treatment with broad spectrum antibiotics that are more toxic and more expensive.³²⁻³³

The cost of care for individual patient also increases due to the need for more costly second line drugs, longer duration of hospital stay, increased need for intensive care and diagnostic testing, higher incidences of complications and expenses incurred by use of isolation precaution.³²

In brief, antibiotic resistance is driving up health care cost, increasing the severity of disease and death rates of some infections. The economic and health costs of resistance, serious enough in the industrialized world, are often more severe in developing countries.³³

Strategies to reduce inappropriate use of antibiotics

Most physicians are aware that antibiotic resistance is an emerging problem created largely by the overuse of antibiotics.³⁴⁻³⁵ This widespread awareness suggests that providing information or education alone will be insufficient to change their prescribing behaviour. Overcoming barriers to more judicious prescribing will require development of materials to support change,

implementation of effective techniques to catalyse such changes, and development of supportive structures in healthcare organizations. Key elements include evidence based recommendations for diagnosis and treatment backed by professional societies, materials for patient education and information to facilitate provider-patient communication. US Centers for Disease Control and Prevention in conjunction with other organizations have developed the intervention strategies for judicious antibiotic use and materials to support such interventions which are discussed in the following section.²⁴

Intervention strategies and approaches²⁴

- **Clinical practice guidelines:** To promote and develop with aid of local authorities.
- **Peer (or small group) education:** To recruit trained and educated personnel who could deliver and cater to the territorial and local needs.
- **Feedback:** The recruited personnel need to gather the feedback from local input and place them for comparison with the standard.
- **Direct mailing of informations and Lectures:** This would help in the flow of relevant information and various opinions of opinion leaders and professional societies.
- **Education of patients and the public:** This is of utmost importance. It helps to increase patient awareness and interest.

MATERIALS²⁴

- Principles of judicious antibiotic use for pediatrics infections.
 - Academic sheets providing one page summaries of the principles of antibiotic use.
 - Posters and pamphlets for educating patients.
 - Question and answer sheets for viral respiratory diagnosis.
 - A "prescription pad" including recommendations for symptomatic treatment for patients with viral respiratory infections.
 - A letter to childcare providers stating that the child can return to day care without an antibiotic.
- Clinical practice guideline for appropriate use of antibiotics must be developed in each community and must be supported by other educational activities.³⁶ Such activities enhance the adoption of clinical practice guidelines if they are actively promoted to clinicians and endorsed by opinion leaders in each community.²⁴
- Many studies have shown that educational/training interventions, whether conducted in large or small groups, can successfully improve targeted antibiotic prescribing

patterns by an average of 20% or more, if they are well designed.^{24, 37} The effectiveness of peer education is enhanced when the message is delivered or endorsed by local opinion leaders and is made relevant to the doctor's own practice.³⁸⁻³⁹ Providing feedback to clinicians regarding their own antibiotic prescribing practices has been a successful technique for achieving behaviour change.⁴⁰ Feedback entails comparisons with peers or with a standard or indicator.²⁴

New communications technologies such as the use of internet enhance the potential to disseminate practice guidelines and provide feedback to clinicians. Computer assisted decision support has been used effectively to improve antibiotic prescription patterns in hospitals and could be extended to outpatient settings.⁴¹ Educating future healthcare providers about the importance of judicious antibiotic use will have long term impact and is a useful adjunct to strategies focused on current providers.²⁴

A multifaceted approach is needed to increase the public's understanding of antibiotic resistance and to change expectations about the use of antibiotics. The key elements should include a public relations campaign, clinic based education, and community outreach activities. A successful public relations effort will require expertise in marketing and communication skills. Educational interventions for patients and parents at outpatient clinics must be an important component of a public education campaign. Educational information can be disseminated through community organizations, schools, childcare centers, and pharmacies. Interventions must be supported by national and local policies that promote judicious antibiotic use. National goals should be developed to reduce unnecessary use, and progress towards those goals should be monitored. Where needed, databases should be established to support feedback interventions and programme evaluation. Economic factors that may affect practices must be carefully considered and, where necessary, modified. Support is also needed to encourage appropriate diagnostic testing.²⁴

Control and prevention

Various guidelines have been published by several societies for optimizing antibiotic use and curtailing antibiotic resistance in hospitals. Key components of these guidelines include.^{23, 42-43}

- Multidisciplinary coordination and cooperation between hospital administrator, clinician, infection control team, microbiologist and hospital pharmacist.
- Formulary based local guidelines on anti-infective therapy and prophylaxis, education and regulation of

prescriptions by consultant specialist, monitoring and auditing drug use, surveillance and reporting of resistance patterns of the hospital flora.

- Detection of patients colonised with communicable resistant bacteria and notification of these to the infection control team when isolation of the patient or decolonization, or both, would be useful.

- Good and regularly updated education on antibiotic use for clinicians, nurses and pharmacists.

- Promotion and monitoring of basic hospital infection control practices such as hand hygiene.

These guidelines are based more on expert opinion and on the results of descriptive and analytical studies than on evidence from controlled trials, which are difficult to design to evaluate these types of population based intervention. Each hospital has its own ecosystem and micro-society, where determinants of antibiotic resistance are quite specific and therefore effective solutions will need to be tailored to local epidemiological circumstances and resources.⁴⁴

Role of Pharmacist in reducing antibiotic resistance

A Pharmacist plays an important role in reducing antibiotic resistance by:

- Counselling of individual patient on appropriate use of antibiotics, such as choice of drug, dose and duration.

- Attending ward rounds and acting as a point of communication between pharmacy, microbiology and infectious disease and infection control teams.

- Preparing evidence based local prescribing guidelines for antibiotics.

- Promoting good prescribing practice.

- Monitoring antibiotic use in terms of volume or 'defined daily dose' and expenditure.

- Providing educational and training program in antibiotic therapy for doctors, nurses, pharmacists and medical and pharmacy students.

Conclusion

The issue of antibiotic misuse is of global concern because of the spreading and developing resistance of most common bacteria to most inexpensive generic antibiotics. Antibiotic resistance now has been universally identified as public health priority and necessary plan of action to combat resistance should be developed. Improving the quality, not just the quantity of medication will require public and professional education towards rational use of antibiotics. Better diagnostic tests, promotion and evaluation of medical and veterinary practice guidelines, restriction of antibiotic use as growth promoters in food

and animals, development of novel antibiotics are some of steps required. Above all, patients, providers and health care leaders must make a serious commitment to change the dynamics of outpatient prescribing. If we want to prove the prediction of an impending post-antibiotic era wrong, the time has come to drastically improve our antibiotic prescribing practices and to strengthen research to identify cost-effective strategies for controlling resistance. If this could be achieved, the care of an individual patient at large can be substantially improved.

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