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Occurance of Anantibiotic Resistance with Their Causes And Effectson Social Health

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ABSTRACT

Antibiotic resistance is a most common global issue which exists on all continents and Affects both low and high income countries or affects both strong and weak health systems. It is a complex problem with numerous consequences for individuals as well as their health-care systems.However development of antibiotic resistance is a natural phenomenon, selection of resistant bacterial strains is driven by antimicrobial use in human and animal sectors.[1],[2] Antibiotic-resistant strains have emerged among both Gram-positive and Gram-negative species. Examples include *Staphylococcus aureus*, *Enterococcus* species, *Pseudomonas aeruginosa*, *Acinetobacter* species, *E-coli*, *Klebsiella pneumoniae*, and*N. gonorrhea*.[3] Antibiotic resistance in *Mycobacterium tuberculosis* has led to the emergence of multi-drug resistant tuberculosis and extensively drug-resistant (XDR) strains causing tuberculosis [4]

Almost all Bacteria differ in terms of their mechanisms by which they develop the antibiotic resistance. Over the last two to three decades, novel mechanisms and dissemination of antibiotic resistance have been observed and identified. The rapid increment of resistant bacteria and other microbes is occurring worldwide, affecting the efficacy of antibiotics, which have transformed medicine and saved millions of lives.[5]-[10] Many decades after the first patients were treated with antibiotics, bacterial infections have again become a threat.[11] The antibiotic resistance crisis has been attributed to the overuse and misuse of these other medications, and lack of new drug development by the pharmaceutical industry due to less economic incentives and high regulatory requirements.

Keywords: AMR, antibiotic use, challenges, drug, resistance

I. INTRODUCTION

An antibiotic is one of an antimicrobial substance which is effective against bacteria and other microbes. Antibiotic medications are widely used in the treatment and prevention of various infectionsand effected by either kill or by inhibit the growth of microbes. There are certain myths about the antibiotic resistance like; antibiotics causes the organism antibiotic resistance or antibiotic resistance organisms are more virulent,but the truth is antibiotic resistance strain appear more virulent because we cannot kill them or stop their growth. In addition, farmers often faced losing large numbers of crops and animals with infectious diseases, leading to serious food shortages, even famine. The discovery and introduction of antibiotics gave us the ability to prevent these tragedies. However, now a day's microorganisms become resistant to antimicrobial treatments, including antibiotics, there is a very real possibility that the drugs we have come to become obsolete. [28][29]

Antibiotics are given to human for treatment and prophylaxis of various infectious diseases, around 80% to 90% of antibiotics are used in outpatients (OPD) and the remainder in hospitals. Antibiotics are appearing to be used not only in excess but also inappropriately and these accounts for approximately 20% to 50 % of all antibiotics used.[45][46]Antibiotic usage resistance rates vary from one country to another country. It is easily 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 also the number of individuals receiving the drug and the population also matters.[47][48] A study suggests that combination of antibiotic use and population majority correlates strongly with the antibiotic resistance in a population than use of the antibiotic alone.[50]

Development of antibiotic resistance was first reported in the animal models in 1940 and simultaneously reported among patients in the 1970s.[51][52] Today drug resistant strains of Mycobacterium tuberculosis are most powerful and

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very threatening to outbreak in one of the world's most prevalent infectious diseases.[53]

Define- Antibiotic resistance

Antibiotic resistance is the ability of bacteria or other microbes to resist or oppose the effects of an **antibiotic**. **Antibiotic resistance** occurs when bacteria or microbes change in such a way that reduces or eliminates the effectiveness of drugs therefore also known as drug resistance.The term antibiotic resistance is a subclass of antimicrobial resistance, is a major concern of overuse of antibiotics. [4]

Antibiotics are the medicines for bacterial infections, Examples of antibiotics: – Penicillin and Ciprofloxacin. Penicillin was discovered by Alexander Fleming in 1928 – Introduced as medicine in the 1940's. Antibiotics can have "broad" or "narrow" spectrum – Broad spectrum: Active against many different types of bacteria – Narrow spectrum: Active against one or a few types of bacteria.

Benefits of antibiotics

Antibiotics have not only saved patient'slives but also played a vital role in achieving major advances in medicine and surgery. They have successfully prevented or treated infections that can occur in patients who are receiving chemotherapy treatments, who have chronic diseases such as diabetes, end-stage renal related disease, or rheumatoid arthritis or who have had complex surgeries such as organ transplants, joint replacements, or cardiac surgery. [22]

Antibiotics have also helped to extend expected life spans by changing the outcome of bacterial infections.[22][23] In 1920, people in the U.S. were expected to live to be only 56.4 years old; now, however, the average U.S. life span is nearly 80 years.Antibiotics have had similar beneficial effects worldwide. In developing countries where sanitation is still poor, antibiotics decrease the morbidity and mortality caused by food-borne and other poverty-related infections. [23]

Difference between antibiotic and antimicrobial resistance is most important, as follows:

- **Antibiotic resistance** refers to bacteria resisting antibiotics.
- **Antimicrobial resistance (AMR)** describes the opposition of any microbe to the drugs that scientists created to kill them.

It is possible for AMR to develop in bacteria, but it can also originate in fungi, parasites, and viruses. This resistance could affect people with *Candida*, malaria, HIV, and a wide range of other conditions.

Antibiotic resistance is defined as the ability of bacteria or other microbes to resist the effects of an **antibiotic**. **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 infections.

Not only the misuse and overuse, but underuse due to lack of access is common in India. Lack of access to good quality, affordable antibiotics leads to significant mortality (especially in children), and hence, there is an urgent need to maximize access and limit excess antibiotic use.[12] Apart from the healthcare sector, antibiotics are also used in livestock such as in animal husbandry, fisheries, and agricultural sectors for therapeutic purposes as well as growth promotion.[13] Environmental pollution by means of pharmaceutical waste, waste from livestock, and hospitals is another dimension contributing to the crisis of antibiotic resistance.[14]

Antibiotic resistant bacteria each year cause approximately more than 38,000 deaths in Thailanda, more than 23,000 deaths in the USA, 25,000 deaths in the European Union. In South Asia (countries like India, Pakistan, Afghanistan, Nepal, Bangladesh) one newborn child dies every 5 minutes from blood stream infections (sepsis) because the antibiotics given are not effective due to bacterial resistance.

WHAT IS RESISTANCE

Resistance is a means the naturally susceptible microorganism acquires ways of not being affected by the drug. Microbial resistance to antimicrobial agents is not a new phenomenon; it has been going on in soil microorganisms since the dawn of time, as competitive/survival mechanisms by microorganisms against other microorganisms. Understanding the mechanisms of resistance is important in order to define better ways to keep existing agents useful for a little longer but also to help in the design of better antimicrobial agents that are not affected by the currently known, predicted, or unknown mechanisms of resistance. Although antimicrobial resistance is a natural biological phenomenon, it often enhanced as a consequence of infectious agents' adaptation to exposure to antimicrobials used in humans or agriculture and the widespread use of disinfectants at the farm and the household levels. It is now accepted that antimicrobial use is the single most important factor responsible for increased antimicrobial resistance.

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INTRINSIC AND ACQUIRED RESISTANCE

1) Intrinsic (natural) Resistance Whereby microbes naturally do not possess target sites for the drugs and therefore the drug does not affect them or they naturally have low permeability to those agents because of the differences in the chemical nature of the drug and the microbial membrane structures especially for those that require entry into the microbial cell in order to affect their action. With intrinsic resistance the organism possesses properties that make it naturally resistant to certain insults, e.g. the more complex outer layer of gram negative bacteria makes it much more difficult for certain antimicrobials to penetrate. Thus intrinsic resistance is considered to be a natural and inherited property with high predictability. Once the identity of the organism is known, the aspects of its anti-microbial resistance are also recognized.

2) Acquired (genetic methods) Resistance Acquired resistance is when a naturally susceptible microbe acquires ways of not being affected by the drug. Any insult, physical or chemical, has the potential to induce changes in the organism. It also consist the chromosomal mutation methods and extra chromosomal plasmid methods.

USE OF ANTIBIOTICS WITH REFERNCE TO RESISTANCE:

Some studies have shown that resistance to antibiotics is directly linked to their usage.It would be important to briefly review the various patterns of antibiotic use. In 2010, India recorded a staggering 12.9 billion units of antibiotic consumption, which was the highest among all the countries.[14] In addition, an increased consumption rate of carbapenems, lincosamides, glycopeptides, linezolid, and daptomycin has been reported in one study.[15] The reasons leading to such situations are multiple, as explained here under [15]-[21]:

1. Ability over the counter. (Pharmacy outlets).
2. Self-medication through hearsay or information gathered from the internet or upon the advice of the shop-keeper;
3. Non-availability and non-utilization of the laboratory service for cultures and antibiotic susceptibility testing;
4. Varying approach of treating doctors – owing to the anxiety of missing a bacterial infection or covering for secondary bacterial infection, lack of up-to-date knowledge on the current revised guidelines and algorithms for antibiotic usage.
5. Incorrect use of antibiotics, simultaneous use of more than a single antibiotic when actually not necessary, not de-escalating when possible, inefficiency in the review of the response to antibiotics.
6. Regulatory issues – Lack of strict implementation of policies (such as schedule H1) and control by the regulatory authorities.
7. Varied perceptions such as perceived demand and expectations among key stakeholders and ethical challenges among healthcare professionals.
8. Unethical commercial practices to promote the sale of antibiotics in large quantities.
9. Use of antibiotics by other non-medical and informal healthcare providers.
10. Lack of community awareness.

FACTORS OF ANTIBIOTIC RESISTANCE

1. Environment factors
- More population and over crowding
- Rapid spread by the better transport facility
- Poor sanitation
- Increase in community acquired resistance
- Ineffective infection control program
- Widespread use of antibiotics in animal husbandry and agriculture and as medical cleansing product

2. Drug related factors
- Over the counter availability of antimicrobials
- Counterfeit and substandard drug causing suboptimal blood concentration
- Irrational fixed dose combination of antimicrobials
- Soaring use of antibiotics

3. Patient related factors
- Poor adherence of dosage regimens
- Poverty
- Lack of sanitation concept
- Lack of education
- Self-medication
- Misconception

4. Prescriber related factor
- Inappropriate use of available drugs
- Increased empiric poly-antimicrobials use
- Overuse of antimicrobials
- Inadequate dosing
- Lack of current knowledge and training

5. Poor clinical practice
- Poor clinical practices that fail to incorporate the pharmacological properties of

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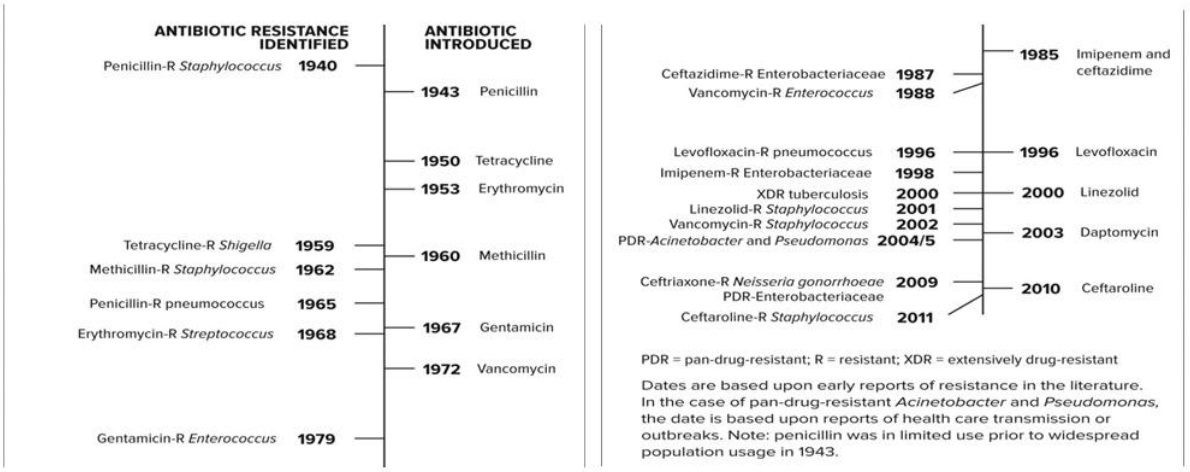
antimicrobials amplify the speed of development of drug resistance.

6. Faulty antibiotic use
- Antimicrobials are over prescribed
- Available without prescription

7. Over prescribed antibiotics
- Clinician should first determine whether antimicrobials therapy is warranted for a given patient.



Mechanism of Antibiotic resistance

The prevention of accumulation of antibiotics either by decreasing uptake, increasing efflux or modification of target molecule of the antimicrobial from the cell.[30]-[41]

Efflux pumps

Membrane proteins that export antibiotics from the cell and maintain their low-intracellular concentrations are called efflux pumps.At the same time, where these antimicrobials are entering in to the cell, efflux mechanisms are pumping them out again, before they reach their target. These pumps are present in the cytoplasmic membrane.Efflux pumps are specific to antibiotics. Most of them are multidrug transporters that are capable to pump a wide range of unrelated antibiotics – macrolides and tetracyclines significantly contribute to multidrug resistant organisms.

Modification of target molecules

Natural variations or acquired changes in the target sites of antibiotics that prevent drug binding is a common mechanism of resistance. Target site changes often result from spontaneous mutation of a bacterial or microbes gene on the chromosome. Since antibiotic interaction with target molecule is generally specific, minor alteration of the target molecule can have important effect on antibiotic binding.

a. Alteration in the 30S subunit or 50S subunit: Of the ribosome leads to resistance to drugs that affect the protein synthesis, i.e., macrolides, tetracycline, chloramphenicol.

b. Alteration in PBP: Modification of the PBP is a favored mechanism in Gram-positive bacteria, whereas production of β-lactamases is a mechanism of resistance for the development of resistance to Gram-negative bacteria. The presence of mutation in penicillin-binding protein leads to a reduced affinity to β-lactam antibiotics. E.g. *Enterococcus faecium* to ampicillin and *Streptococcus pneumoniae* to penicillin

c. Altered cell wall precursors: Cell wall synthesis in Gram-positive bacteria can be inhibited by glycopeptides, e.g., vancomycin or teicoplanin, by their binding to D-alanyl-D-alanine residues of peptidoglycan precursors.

d. Mutated-DNA gyrase and topoisomerase IV leads to FQ resistance: Quinolones bind to DNA gyrase A subunit. The mechanism of resistance involves the modification of two enzymes: DNA gyrase (coded by genes gyr A and gyr B) and topoisomerase IV (coded by genes par C and par E).

e. Ribosomal protection mechanisms imparting resistance to tetracyclines

f. RNA polymerase mutations conferring resistance to rifampicin.

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Porins and their role in outer membrane permeability

Besides active efflux of antibiotics, bacteria and other microbes can reduce the intracellular concentration of these harmful compounds by preventing their influx. The cell wall and membrane of bacteria function as a barrier to the outer environment, excluding toxic compounds. Gram-negative bacteria are especially impermeable to many compounds, including antibiotics, owing to the composition of their own cell envelope, which consists of an inner membrane, a small periplasmic space and an outer membraneadditionally.[42]

Resistance Due to Anthropogenic Activities

The important role of human activities in the generation of environmental reservoirs of antibiotic resistance cannot be disputed. Since the 1940s, the increasing amounts of antibiotics designated for human applications have been manufactured, used clinically, released into the environment thus providing constant selection and maintenance pressure for populations of resistant strains in all environments. Obtaining accurate figures on the quantities of antimicrobials produced by the pharmaceutical industry is difficult but it can be estimated that many millions of metric tons of antibiotic compounds have been released into the biosphere over the last half-century. Since the available evidence illustrate that little in the way of antibiotics is contributed by naturally occurring antibiotic-producing strains in their native environments. Some alternative uses of antimicrobial agents are as follows: [43]

- Growth promotion/prophylactic use in animals;
- Therapeutic/prophylactic use in humans;
- Therapeutic/prophylactic use in marine culture;
- Therapeutic/prophylactic use in household pets;
- Pest control/cloning for plants and agriculture;
- Applicability as biocides in toiletries and in hand care and household cleaning products; and
- Culture sterility, cloning, and selection in research and industry

Examples

Methicillin-Resistant Staphylococcus Aureus

MRSA was first identified five decades ago. Since then, MRSA infections have spread worldwide, appearing at a high incidence in several countries in Europe, the Americas, and the Asia-Pacific region. In the U.S., 11,285 deaths per year have been attributed to MRSA alone.MRSA is resistant to penicillin-like beta-lactam antibiotics. Fortunately, the incidence of MRSA infections seems to be declining, since aggressive preventive hygiene measures in hospitals in some areas (like the Netherlands and United Kingdom) have had a positive effect. Between 2005 and 2011, overall rates of invasive MRSA dropped 31%; the largest declines (around 54%). [25]

Vancomycin-Resistant Enterococci

VRE presents a major therapeutic challenge.Enterococci cause a wide range of illnesses.VRE infections often caused by *Enterococcus faecium* and less frequently by *Enterococcus faecalis*, have a lower prevalence and epidemiological impact than MRSA does worldwide, except for the U.S. and some European countries. An estimated 66,000 HAI Enterococci infections occur in the U.S. each year. The proportion of infections that are vancomycin-resistant depends on the species. Overall, 20,000 (30%) of hospital-acquired enterococcal infections per year are vancomycin-resistant, leading to 1,300 deaths.

Drug-Resistant *Streptococcus pneumonia*

S. pneumonia can cause more serious and sometimes life- threatening infections. It is a major cause of bacterial pneumonia and meningitis, as well as bloodstream, ear, and sinus infections. Resistant *S. pneumoniae* infections complicate medical treatment, resulting in nearly 1.2 million illnesses and 7,000 deaths per year. The majority of these cases and deaths occur among adults 50 years of age or older, with the highest rates among those 65 years of age or older. *S. pneumoniae* has developed resistance to drugs in the penicillin class and erythromycins, such as amoxicillin and azithromycin, respectively.It has also developed resistance to less commonly used drugs. In 30% of severe *S. pneumoniae* cases, the bacteria are fully resistant to one or more clinically relevant antibiotics.[27]

***Drug-Resistant* Mycobacterium Tuberculosis**

Drug-resistant *M. tuberculosis* infections are a serious threat in the U.S. and an even more urgent threat worldwide. The WHO reported that in 2012, 170,000 people died from drug-resistant tuberculosis (TB) infections. *M. tuberculosis* is most commonly spread through the air. Infections caused by this bacterium can occur anywhere in the body but most often appear in the lungs. Of a total of 10,528 TB cases reported in the U.S. in 2011, antibiotic resistance was identified in 1,042, or 9.9%.

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Carbapenem-Resistant Enterobacteriaceae (CRE)

Carbapenem-resistant Enterobacteriaceae (CRE) are a group of bacteria that have become resistant to "all or nearly all" available antibiotics, including carbapenems, which are typically reserved as the "treatment of last resort" against drug-resistant pathogens. An enzyme called New Delhi metallo-beta-lactamase (NDM-1) is present in some gram-negative Enterobacteriaceae bacteria (notably *Escherichia coli* and *K. pneumoniae*) that make them resistant to virtually all beta-lactams, including carbapenems.

***MDR* Pseudomonas Aeruginosa**

P. aeruginosa is a common cause of HAIs, including pneumonia and bloodstream, urinary tract, and surgical-site infections. More than 6,000 (13%) of the 51,000 health care–associated *P. aeruginosa* infections that occur in the U.S. each year are MDR. Roughly 400 deaths per year are attributed to these infections.

***MDR* Acinetobacter**

Acinetobacter is a gram-negative bacterium that causes pneumonia or bloodstream infections, especially in critically ill patients on mechanical ventilation.[5] Some *Acinetobacter* species have become resistant to all or nearly all antibiotics, including carbapenems, which are often considered to be the drug of last resort.[5] About 12,000 health care–acquired *Acinetobacter* infections occur in the U.S. each year.

***Drug-resistant* Neisseria gonorrhea**

In recent years, drug-resistant forms of *N. gonorrhoeae*, the causative agent for the sexually transmitted disease gonorrhea, have begun to emerge in the U.S. The CDC estimates that more than 800,000 cases of gonorrhea occur annually, making it the second-most-frequently reported infectious disease in the U.S. Should drug-resistant *N. gonorrhea* become more widespread, it has been estimated that it would cause 75,000 additional cases of pelvic inflammatory disease, 15,000 cases of epididymitis, and 222 additional human immunodeficiency virus infections over a projected 10-year period. [26]

TREATMENT OPTION FOR SELECTED HIGHLY RESISTANCE BACTERIA

Sr. no.	Organism	Resistance	Antibiotic used
1	E. Faecalis	Penicillin	Vancomycin, Ampicillin-SLB
2	MRSA	Methicillin, Vancomycin	Linezolid, Quinpristine, Dalfopristine, Daptomycin, Telavacin
3	S. Epidermidis	Methicillin	Vancomycin + Rifampicin + Gentamicin
4	S. Pneumonia	Penicillin G	Ceftriaxone, Cefotaxime, Telithromycin, Vancomycin + Rifampicin
5	C. Jejuni	_____	Macrolids, Doxycycline, Clindamycin
6	E. Coli	Cotrimazole, Cephalosporins	Fosfomycin, Nitrofurantoin, Ertapenum
7	K. Pneumoniae	Cephalosporin, Ceftazidime	Imipenum, Meropenum, Colistin
8	P. aeruginosa	Imipenum, Meropenum	Antipseudomal, aminoglycosides, Colistin, Ceftazidime

ROLE OF PHARMACIST IN REDUCING ANTIBIOTIC RESISTANCE[54]

- A Pharmacist plays an important role in reducing antibiotic resistance by Counseling of individual patient on appropriate use of antibiotics, such as choice of drug, dose and duration and side effect related to that.
- Attending ward, seminar, rounds and acting as a midpoint of communication between pharmacy, physician, microbiology and infectious disease and infection control teams.
- Preparing evidence based on the local prescribing guidelines for antibiotics and their application.
- Promoting good prescribing practice or error free practice.
- Monitoring the 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.

ANTIBIOTIC RESISTANCE EFFECT ON ECONOMIC

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Antibiotic-resistant infections are a substantial health and economic burden to the health care system of almost all the countries.[1] This is commonly occurs in hospitals, due to the clustering of highly vulnerable patients, extensive use of invasive procedures, and high rates of antibiotic use in this setting.[1] Nearly two million Americans per year develop HAIs, resulting in 99,000 deaths, most due to antibacterial-resistant pathogens.[1] In 2006, two common HAIs (sepsis and pneumonia) were found to be responsible for the deaths of nearly 50,000 Americans and cost the U.S. health care system more than $8 billion.

Antibiotic-resistant infections add considerable costs to the nation's already overburdened health care system. When first-line and then second-line antibiotic treatment options are limited or unavailable, health care professionals may be forced to use antibiotics that are more toxic to the patient and frequently more expensive.[24] Even when effective treatments exist, data show that in most cases patients with resistant infections require significantly longer hospital stays, more doctors visits, and lengthier recuperations and experience a higher incidence of long-term disability. The duration of hospital stays for patients with antibiotic-resistant infections was found to be prolonged by 6.4 to 12.7 days, collectively adding an extra eight million hospital days.

Estimates regarding the medical cost per patient with an antibiotic-resistant infection range from $18,588 to $29, 069. [24] The total economic burden placed on the U.S. economy by antibiotic-resistant infections has been estimated to be as high as $20 billion in health care costs and $35 billion a year in lost productivity.[1] Antibiotic-resistant infections also burden families and communities due to lost wages and health care costs. [24]

FACTORS DRIVING ANTIBIOTIC RESISTANCE IN INDIA

Antibiotic consumption in Humans In 2014, India was the highest consumer of antibiotics, followed by China and the United States. However, the per capita consumption of antibiotics in India is much lower than in several other high-income countries. Some of the reasons for high resistance rates in India are discussed in this section.

High consumption of broadspectrum antibiotics is those that are effective against a wide range of disease-causing bacteria, in contrast to narrow-spectrum antibiotics, which are effective against specific families of bacteria. From 2000 to 2015, cephalosporin and broad-spectrum penicillin consumption increased rapidly, whereas narrow-spectrum penicillin consumption was low and decreasing. The rapid increase of third-generation cephalosporin consumption could be attributed to multiple factors, such as increasing resistance to fluoroquinolones among bacteria causing enteric fever and bacterial dysentery, making third-generationcephalosporin's empiric treatment choices for these two common infections. Changing prescribing practices by healthcare providers, with third-generation cephalosporin's being substituted for penicillin's in the treatment of upper respiratory tract infections in outpatient settings and lower respiratory tract infections in inpatient settings. Another factor is a lack of widespread availability of narrow-spectrum agents such as first-generation penicillin's (penicillin G, benzathine penicillin) in contrast to third-generation cephalosporin's in the pharmacies. In India, only one Formulation Company is making penicillin G or benzathine penicillin, whereas 135 formulation companies manufacture cefixime, a third-generation cephalosporin.

Antibiotic fixed-dose combinations Antibiotic fixed-dose combinations (FDCs) are combinations of two or more active antibiotics in a singledosage form. Antibiotic FDCs should be prescribed when the combination has a proven advantage over single compounds administered separately in therapeutic effect, safety, or compliance. However, in India, antibiotic FDCs are heavily prescribed even without the knowledge of a proven advantage over single compounds. Injudicious use of antibiotic FDCs could lead to emergence of bacterial strains resistant to multiple antibiotics. Approximately 118 antibiotic FDCs are available in India.

Social Factors Several social factors drive inappropriate antibiotic use in India. Among the general public, such factors include self-medication, access to antibiotics without prescription, use of pharmacies and informal healthcare providers as sources of healthcare, and lack of knowledge about when to use antibiotics.

INTERVENTION STRATEGIES AND APPROACHES[54][55]

- Implement new and modified Clinical practice guidelines: To promote and develop with aid of local authorities.
- Peer 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 information 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 toward their health.

II. CONCLUSION

Rapidly increase in the resistant bacteria and other microbes threaten the extraordinary public or social health benefits that have been achieved with the antibiotics. This crisis is now globally affects, reflecting the worldwide overuse and misuse of these drugs and the lack of development of new antibiotic agents in research & development department by pharmaceutical companies to possess the challenges and approaches. Antibiotic-resistant infections produce a substantial health and economic burden on the social health care system. Coordinated efforts to implement new modified policies, renew research efforts, and pursue steps to manage the crisis are strongly needed. Progress in these areas, as well as new agents to treat bacterial infections, will be required for the future aspects to minimizing the adverse effects and to save the life of an individual.

The current estimation of antibiotic discovery is not sufficient to combat antibiotic resistance, it is required to develop the alternate strategies. In this regard, antibacterial compounds that are not standalone drugs but are synergistic with the conventional antibiotics would be a step forward. [44]

REFERANCES:

[1]. Bell BG, Schellevis F, Stobberingh E, Goossens H, Pringle M. A systematic review and meta-analysis of the effects of antibiotic consumption on antibiotic resistance. BMC Infect Dis [Internet]. 2014;14:13.

[2]. Aarestrup FM, Kruse H, Tast E, Hammerum AM, Jensen LB. Associations between the use of antimicrobial agents for growth promotion and the occurrence of resistance among Enterococcus faecium from broilers and pigs in Denmark, Finland, and Norway. Microb Drug Resist Larchmt *N* 2000;6:63-70.

[3]. Kumar SG, Adithan C, Harish BN, Sujatha S, Roy G, Malini A. Antimicrobial resistance in India: A review. J Nat SciBiol Med 2013;4:286-91. WHO | Global tuberculosis report 2016 [Internet].

[4]. WHO [cited 2017 Sep 10]. Available from: http://www.who.int/tb/publications/global_report/en/.

[5]. Golkar Z, Bagazra O, Pace DG. Bacteriophage therapy: a potential solution for the antibiotic resistance crisis. J Infect Dev Ctries. 2014;8(2):129–136. 13.

[6]. Gould IM, Bal AM. New antibiotic agents in the pipeline and how they can overcome microbial resistance. Virulence. 2013;4(2):185–191.

[7]. Wright GD. Something new: revisiting natural products in antibiotic drug discovery. Can J Microbiol. 2014;60(3):147–154.

[8]. Sengupta S, Chattopadhyay MK, Grossart HP. The multifaceted roles of antibiotics and antibiotic resistance in nature. Front Microbiol. 2013;4:47.

[9]. Centers for Disease Control and Prevention, Office of Infectious Disease Antibiotic resistance threats in the United States, 2013. Apr, 2013. Available at: http://www.cdc.gov/drugresistance/threat-report-2013. Accessed January 28, 2015.

[10]. Congressional Research Service Report Life expectancy in the United States. Mar, 2005. Available at: http://www.cnie.org/nle/crsreports/05mar/RL32792.pdf. Accessed January 5, 2015.

[11]. Spellberg B, Gilbert DN. The future of antibiotics and resistance: a tribute to a career of leadership by John Bartlett. Clin Infect Dis. 2014;59 (suppl 2):S71–S75.

[12]. Mendelson M, Røttingen JA, Gopinathan U, Hamer DH, Wertheim H, Basnyat B, *et al.* Maximising access to achieve appropriate human antimicrobial use in low-income and middle-income countries. Lancet LondEngl 2016;387:188-98.

[13]. A game of chicken: How Indian poultry farming is creating global superbugs [Internet]. Bur. Investig J[cited 2019 Mar 22]. Available from: https://www.thebureauinvestigates.com/stories/2018-01-30/a-game-of-chicken-how-indian-poultry-farming-is-creating-global-superbugs.

[14]. Westphal-Settele, Konradi K, Balzer S, Schonfeld J. [The environment as a reservoir for antimicrobial resistance : A growing

problem for public health?]. Bundes gesundheitsblattGesundhe its for schungGesundhe it's for schutz2018;61:533-42.

[15]. Boeckel TPV, Gandra S, Ashok A, Caudron Q, Grenfell BT, Levin SA, *et al*. Global antibiotic consumption 2000 to 2010: An analysis of national pharmaceutical sales data. Lancet Infect Dis 2014;14:742-50.

[16]. Farooqui HH, Selvaraj S, Mehta A, Heymann DL. Community level antibiotic utilization in India and its comparison vis-à -vis European countries: Evidence from pharmaceutical sales data. PLoS One2018;13:e0204805.

[17]. Om C, Daily F, Vlieghe E, McLaughlin JC, McLaws ML. "If it's a broad spectrum, it can shoot better": Inappropriate antibiotic prescribing in Cambodia. Antimicrobial Basu S, Garg S. Antibiotic prescribing behavior among physicians: Ethical challenges in resource-poor settings. J Med Ethics Hist Med 2018;11:5.

[18]. Imanpour S, Nwaiwu O, McMaughan DK, DeSalvo B, Bashir A. Factors associated with antibiotic prescriptions for the viral origin diseases in office-based practices, 2006–2012. JRSM Open 2017;8:8.

[19]. Hashemi S, Nasrollah A, Rajabi M. Irrational antibiotic prescribing: A local issue or global concern?. EXCLI J 2013;12:384-95.

[20]. Laxminarayan R, Chaudhury RR. Antibiotic resistance in India: Drivers and opportunities for action. PLoS Med 2016;13:e1001974.

[21]. Chandy SJ, Mathai E, Thomas K, Faruqui AR, Holloway K, Lundborg CS. Antibiotic use and resistance: Perceptions and ethical challenges among doctors, pharmacists and the public in Vellore, South India. Indian J Med Ethics 2013; 10:20-7.

[22]. Piddock LJ. The crisis of no new antibiotics—what is the way forward? Lancet Infect Dis. 2012; 12(3):249–253.

[23]. Rossolini GM, Arena F, Pecile P, Pollini S. Update on the antibiotic resistance crisis. Clin Opin Pharmacol. 2014; 18:56–60.

[24]. Michael CA, Dominey-Howes D, Labbate M. The antibiotic resistance crisis: causes, consequences, and management. Front Public Health. 2014; 2:145.

[25]. Gross M. Antibiotics in crisis. Curr Biol. 2013; 23(24):R1063–R1065.

[26]. Unemo, Magnus; Jensen, Jorgen S. (10 January 2017). "Antimicrobial-resistant sexually transmitted infections: gonorrhoea and *Mycoplasma genitalium*". *Nature Reviews Urology*. **14** (3): 139–125. doi:10.1038/nrurol.2016.268. PMID 280 7240

[27]. Albrich WC, Monnet DL, Harbarth S (2004). "Antibiotic selection pressure and resistance in Streptococcus pneumoniae and Streptococcus pyogenes". *Emerg. Infect. Dis*. **10** (3): 514–7. doi:10.3201/eid1003.030252. PMC 332280 5. PMID 15109426.

[28]. Chief Medical Officer annual report: volume 2 https://www.gov.uk/government/publications/chief-medical-officer-annual-report-volume-2.

[29]. Antimicrobial resistance: global report on surveillance 2014 http://www.who.int/drugresistance/documents/surveillancereport/en/.

[30]. Grundmann H, Aires-de-Sousa M, Boyce J, Tiemersma E. Emergence and resurgence of meticillin-resistant *Staphylococcus aureus* as a public-health threat. Lancet 2006;368:874-85.

[31]. Yoneyama H, Katsumata R. Antibiotic resistance in bacteria and its future for novel antibiotic development. Biosci Biotechnol Biochem 2006;70:1060-75.

[32]. Johnston NJ, Mukhtar TA, Wright GD. Streptogramin antibiotics: Mode of action and resistance. Curr Drug Targets 2002;3:335-44.

[33]. Vannuffel P, Cocito C. Mechanism of action of streptogramins and macrolides. Drugs 1996;51 Suppl 1:20-30.

[34]. Lambert PA. Bacterial resistance to antibiotics: Modified target sites. Adv Drug Deliv Rev 2005;57:1471-85.

[35]. Wise R. A review of the mechanisms of action and resistance of antimicrobial agents. Can Respir J 1999;6 Suppl A:20A-2A.

[36]. Bozdogan B, Appelbaum PC. Oxazolidinones: Activity, mode of action, and mechanism of resistance. Int J Antimicrob Agents 2004;23:113-9.

[37]. Higgins PG, Fluit AC, Schmitz FJ. Fluoroquinolones: Structure and target sites. Curr Drug Targets 2003;4:181-90.

[38]. Tenover FC. Mechanisms of antimicrobial resistance in bacteria. Am J Med 2006;119 6 Suppl 1:S3-10.

[39]. Lambert PA. Mechanisms of antibiotic resistance in *Pseudomonas aeruginosa*. J R Soc Med 2002;95 Suppl 41:22-6.
[40]. Hiramatsu K, Cui L, Kuroda M, Ito T. The emergence and evolution of methicillin-resistant *Staphylococcus aureus*. Trends Microbiol 2001;9:486-93.
[41]. Alekshun MN, Levy SB. Molecular mechanisms of antibacterial multidrug resistance. Cell 2007;128:1037-50.
[42]. Knopp, M. 2018. Mechanisms of Antibiotic Resistance Evolution. Digital Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine 1477. 59 pp. Uppsala: Acta Universitatis Upsaliensis. ISBN 978-91-513-0384-0.
[43]. Julian Davies* and Dorothy Davies "Origins and Evolution of Antibiotic Resistance" MICROBIOLOGY AND MOLECULAR BIOLOGY REVIEWS, Sept. 2010, p. 417–433 Vol. 74, No. 3 1092-2172/10/$12.00 doi:10.1128/MMBR.00016-10.
[44]. Anushya Petchiappan, Dipankar Chatterji, "Antibiotic Resistance: Current Perspective" *ACS Omega* 2017, 2, 10, 7400-7409, Publication Date:October 30, 2017.
[45]. Cizman M. The use and resistance of antimicrobials in the community. Int J Antimicrob Agents 2003; 21: 297-307.
[46]. Wise R, Hart T, Cars O. Antimicrobial resistance is a major threat to public health. BMJ 1998; 317: 609-610.
[47]. Sorensen TL, Monnet D. Control of antibiotic use in the community: The Danish experience. Infect Control Hosp Epidemiol 2000; 21: 387-389.
[48]. Bremon RA, Ruiz Tovar M, Gorricho PB, Diaz de Torres P, Rodriguez R. Non -hospital consumption of antibiotics in Spain: 1987-1997. J Antimicrob Chemother 2000; 45: 395- 400.
[49]. Leegaard TM, Bevanger L, Jureen R. Antibiotic sensitivity still prevails in Norweigan blood culture isolates. Int J Antimicrob Agents 2001; 18: 99-106.
[50]. Levy SB. Antibiotic resistance: Consequences of inaction. Clin Infect Dis 2001; 33: 124-129.
[51]. Frisch AW, Price AE, Myers GB. Type VIII Pneumococcus: Development of sulfadiazine resistance transmission by cross infection and persistence in carriers. Ann Intern Med 1943; 18:271-278.
[52]. Cates KL, Gerard JM, Giebink GS. A penicillin-resistant pneumococcus. J Pediatr 1978; 93: 624-626.
[53]. Bari SB, Mahajan BM, Surana SJ. Resistance to antibiotic: A challenge in chemotherapy. Indian Journal of Pharmaceutical Education and Research 2008; 42 (1): 3-11.
[54]. Alok Katiyar, Rajat Singh, Piyush Mittal "ANTIBIOTIC RESISTANCE –A GLOBAL ISSUE OF CONCERN REKHA BISHT", Asian Journal of Pharmaceutical and Clinical Research, Volume 2, Issue 2, April- June, 2009.
[55]. Belongia EA, Schwartz B. Strategies for promoting judicious use of antibiotics by doctors and patients. BMJ 1998; 317: 668-671.