IS ANTIBIOTICS ARE BECOMING A THREAT TO OUR FUTURE GENERATIONS ?

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ABSTRACT

Antibiotics are considered as essential tool in curing various diseases because of their safety, efficacy and better outcomes. Due to over exploitation of antibiotics, microbes are becoming resistant, multi-resistant and non-resistant. Developing a new antibiotic requires more time as well as more expenditure, while using accessible antibiotics judiciously and rationally offers potential for future generations. Antibiotics presence can be detected in our daily drinking water due to our poor control of their use, and medical professionals and government have an imperative role in improving the use of antibiotics.

KEYWORDS

Antibiotics, antibiotic resistance, antimicrobial agent, microorganisms, environmental issues with antibiotics

1. INTRODUCTION

Antibiotic are considered as magic medication in the modern medicine. Use of antibiotics becomes a routine practice for various ailments. In hospitals, antibiotics are most commonly prescribed, due to its irrational, injudicious and excessive usage consequently lead to antimicrobial or antibiotic resistance. Selection of antibiotics in a judicious way requires proper clinical decision as well as very intense knowledge regarding microbiological details, pharmacokinetic and pharmacodynamics information, skills through education and experience [1]. But antibiotics are used in destitute mode even without considering resistance [2]. Various reports illustrate, irrational use of antibiotics causing infections are worse or perilous than the originally diagnosed infections [3].

Antibiotics are generally used in two ways empirical therapy, evidence based therapy/definitive therapy. For the initial therapy or empirical therapy, antibiotics are prescribed as broad spectrum antibiotics or combination therapy of antibiotics. Since, disease causing microorganism is not identified thus antibiotic must cover the entire organism to prevent that particular infection. In case of definitive therapy, microorganism is identified by the various tests. Hence, a regimen with narrow spectrum, less side effects, low toxicity can be prescribed for a flawless therapy [1]. Antimicrobial agent acts as in dual ways, by saving lives as well as forming superbugs to create new infectious diseases.

Data's were collected from reviewing various articles from Google scholar, Google, Research gate, Pub med, Elsevier, Springer using keywords like antibiotics, antibiotic use in veterinary, aquatic cultures, antibiotic resistance, problems associated with antibiotic resistance, antibiotic resistance, antibiotic culture sensitivity and relevant information's were taken from various articles and excluded abstracts.

USES OF ANTIBIOTICS

Antibiotics are extensively used for humans, animal rearing, tissue cultures, food preservatives, aquatic animals and plants [4]. Antibiotics are used in injudicious manner in animal rearing, which are not used for disease condition, but used as growth promoters as well as for prophylactic therapy. Antibiotics are basically prescribed for infection present in gastrointestinal, intra-abdominal, central nervous system (CNS) infections, ear and eye infections, neonatal and paediatric infections, skin and soft tissue infection, surgical prophylaxis [5].

FACTORS FOR SELECTION OF AN ANTIMICROBIAL AGENT

- Sensitivity pattern of the organism
- Location and severity of infection which may determine route of administration
- Ability of Patient to eliminate the drug for estimating renal and hepatic function
- Patients age, gender, pregnancy status, allergies, CNS disorder, genetic factors, pre-existing medical problems [6].

BACTERIAL IDENTIFICATIONS

- Based on the staining method, shape and oxygen use activities bacteria's can be differentiated.
- Staining Method - Gram positive and Gram negative bacteria
- Based on oxygen usage - Aerobic bacteria which requires oxygen
- Anaerobic bacteria which doesn't require oxygen.

Based on the shape - Bacilli, cocci, spirilla which are rod, sphere and spiral shapes respectively[7].

On the basis of spectrum of activity, antibiotics can be classified as narrow, broad and extended spectrum of activity. Narrow spectrum includes Streptomycin, Erythromycin. Broad spectrum includes Chloramphenicol, Tetracyclines. Antibiotics can be bacteriostatic as well as bactericidal. For example, Clindamycin, Linezolid, Ethambutol, Tetracyclines, Nitrofurantoin, Tigecycline, Trimethoprim, Erythromycin are Bacteriostatic antibiotics whereas Penicillins, Isoniazid, Aminoglycosides, Vancomycin, Metronidazole, Cephalosporins, Ciprofloxacin are antibiotics with bactericidal action. Based on the concentration of antibiotics bacteriostatic antibiotics can act as bactericidal and vice versa [8].

2. TARGET TISSUE PENETRATION OF ANTIBIOTICS

Aminoglycosides have good penetration in urinary tract (if normal GFR), fair in soft tissues, poor penetration in Cerebrospinal fluid (CSF), lungs. Ampicillin and ceftriaxone antibiotics are having good penetration in lungs, soft tissues, urinary tract and high concentration can penetrate in CSF. Meropenem in high concentration have good penetration in CSF, good penetration in lungs, soft tissues and urinary tract. Linezolid is having good penetration in CSF, lungs, soft tissues, urinary tract. Vancomycin is having good penetration in urinary tract, fairly in lungs and poor penetration in CSF and soft tissues[9].

NORMAL MICROORGANISMS IN OUR BODY

Normal flora of microorganisms can be observed in our body. In skin organisms like *Staphylococcus epidemidis, S. aureus, Micrococci*, in mouth, anaerobic oral organisms, *Viridans*

streptococci, in upper respiratory tract *Streptococcus pneumoniae, Staphylococcus, Neisseria, Haemophilus sp*. Stomach organisms like *Streptococcus, Lactobacillus*, in small intestine *Enterococcus, Enterobacteriacae, Lactobacillus, Clostridium sp*. and in large intestine *Enterobacteriaceae, Pseudomonas sp., Enterococcus sp., Streptococccus sp.*. Infections can emerge from the same individual, by normal flora which is referred as endogenous infection. Hence, it is important to identify the normal flora as well as disease causing organism which otherwise may lead to resistant bacteria by antimicrobial therapy[10].

HOW ANTIBIOTICS CAN ENTER OUR ECOSYSTEM

Unwanted, unused or expired medications can be flushed in toilets, washed in washbasins or thrown in trash bin can reach our environment via soil, water systems. Animals or human beings treated with antibiotics, medication may not be completely metabolised presence of these antibiotics can be seen in urine and faeces of animals and humans [11,12,13]. Industrial or Manufacturing companies untreated water or waste which contains antibiotics also reach to the environment[14].

HALF-LIFE OF ANTIBIOTICS IN THE ENVIRONMENT

To estimate the antibiotics half-life or degradation period from environment it is often a difficult task. Since antibiotics have various origins like human use, veterinary use and from manufacturers. Some antibiotics degrade easily while others remain in their original state for a long duration in our environment [15].

Various literature illustrates, antibiotics like Penicillin's are degraded easily, at the same time when we compare other antibiotics like Macrolides (Tylosin), Fluroquinolones (Ciprofloxacin), Tetracycline's remain longer in our environment by accumulating in higher concentration[16,17].

SIGNIFICANCE OF CULTURE SENSITIVITY

Based on the experience, region or location, clinicians usually prescribe antibiotics empirically. In case of severe illness or chronic infections clinicians usually prefer culture or antibiotic susceptibility testing. An organism considered to be susceptible to antibiotic, its growth must be inhibited at a concentration less than the plasma concentration achievable using the labelled dose given by the Manufacturer [18]. The choice of antibiotic by the clinician should be always bacteria or an organism which is susceptible to an antibiotic and avoid the intermediate and resistant. An antibiotic with Minimum Inhibitory Concentration (MIC) is more useful and for the better treatment antibiotics with MIC lower than the achievable plasma concentration should be considered [19]. Antibiotic effect will be stronger, when MIC is lower. Various methods like Agar dilution method, Broth dilution method, Disk- diffusion method or Kirby- Bauer methods these methods are easy and less expensive[20,21].

Based on the culture sensitivity test data, antibiotic selection is often difficult as these datas, does not provide complete guarantee in clinical success. Bacteria present in the site of infection may be higher than the antibiotic susceptibility thus, chance of reduced effect of medication can be observed. False positive result may occur in case of normal flora or nosocomial organisms isolated from the site or if the samples were aseptically, improperly collected, stored and cultured. Hence, various variables like site and severity of infection, patient age, allergies, pre-existing medical conditions, medication pharmacokinetic and pharmacodynamics data's, cost of therapy is required for choosing the best antibiotic for the treatment[18].

SYNERGISTIC EFFECTS OF ANTIBIOTICS IN OUR ECOSYSTEM

The synergistic effects in our ecosystem by antibiotics and various other active pharmaceutical agents are unimaginable. In aquatic system, antibiotics like Quinolones, Sulphonamides and Trimethoprim are more observed [22]. Studies reveals a petrifying issue that is, antibiotics are affecting Nitrogen cycle [23, 24]. Effect on nitrogen transformation, organic matter degradation, nutrient cycles, methanogenesis, sulphate reduction [25].

FACTORS WHICH ARE AFFECTING DEVELOPMENT AND SPREAD OF RESISTANCE

Irrational prescription, easily available over the counter (OTC) antibiotics, non-adherence, pollution, travelling, poverty, irrational veterinary use, excessive usage of antibacterial products like soaps, ointments, counterfeit medications, sub therapeutic doses, less duration of treatment, problems associated with the dosage intervals etc., are certain elements which are contributing to development and spread of antibiotic resistance.

3. RESISTANCE

Natural selection is a common phenomenon in which the organisms adapt for its better survival. Even without human being's interference this process already exists for microorganisms, animals and human beings and all other inhabitants in our universe [26]. Beyond this, our human population is playing a domineering role in antibiotic resistance.
The Reservoir hypothesis says regarding the selective pressure, an antibiotic resistance came into existence after an antibiotic therapy, it will inhibit or kill infectious organism as well as normal flora, a decline in the population of susceptible bacteria, naturally resistant bacteria begins to generate, developing a reservoir of antibiotic resistant bacteria [27].

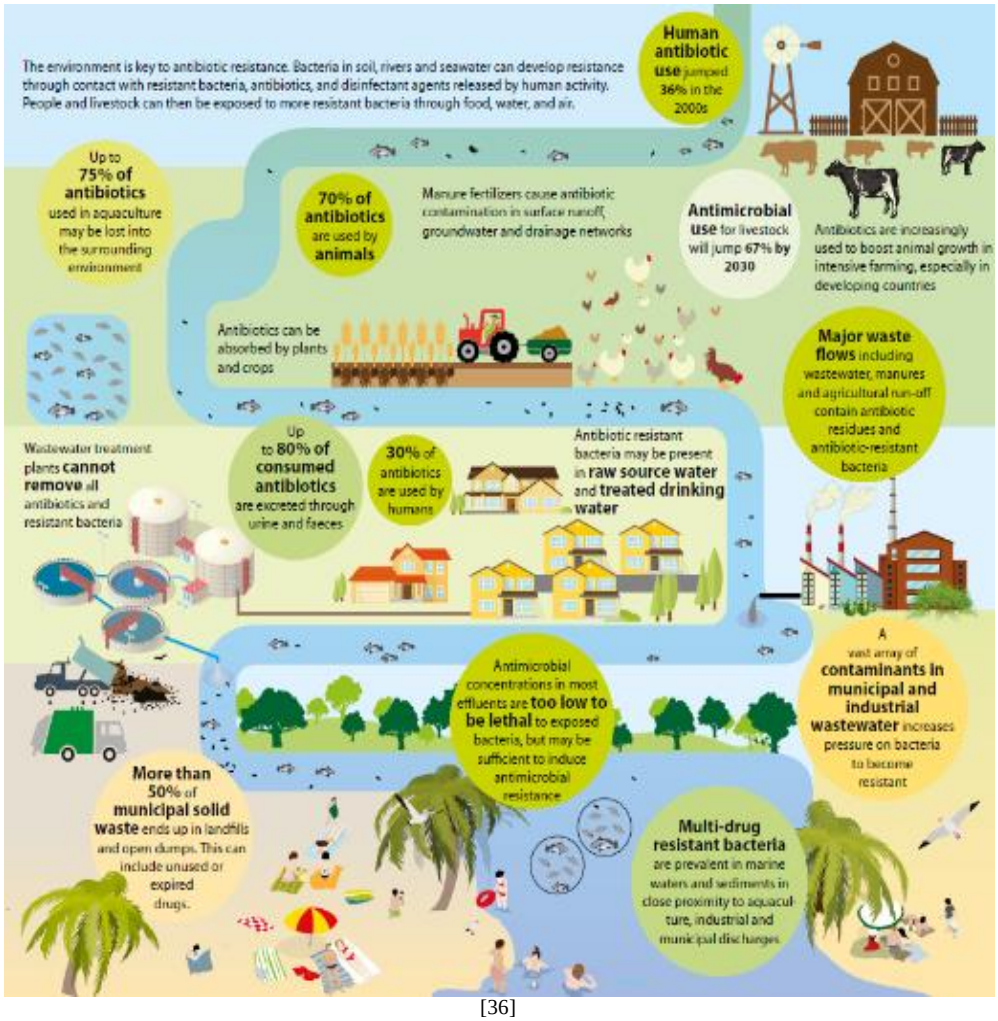
After consumption of antibiotics, complete metabolism may not happen, it can be excreted via urine or faeces, then it enters our environment via water and soil later, it enters into our food chain hence, by direct or indirect contact chance of antibiotics resistance emerges. To illustrate this petrifying condition, a study conducted in United Kingdom (UK) coastal recreational waters, a 6 million exposure event to *E. coli* antibiotic resistance found [28].

Municipal waste water contains the presence of various pharmaceutical items like flushed, improperly disposed antibiotics and other medications, hospital related waste with high content of disinfectants, antibiotics, hand sanitizers etc., certain pharmaceutical companies discard their waste by improperly treating, it may have large concentration of antibiotics and its reagents for preparations[29].

According to the Washington Times, waste water collected from South Indian industrial regions showed the presence of antibiotics like Ciprofloxacin, Ofloxacin, Moxifloxacin which was even more toxic ecosystem over there [30]. In China, a state owned company had discarded untreated antibiotic waste into Huto river which contains Penicillin, Amoxicillin, Streptomycin and Cefradine [31].

The European Centre for Disease Prevention and Control reports significant increase in the *Klebisella pneumonia* organism's percentage resistance to various antibiotics like Fluroquinolones, Aminoglycosides and Third generation Cephalosporins [32]. In certain regions of China, pigs were routinely given with Colistin antibiotics, studies reveal that Colistin resistant bacteria's are observed in China. They observed Colistin resistant *E.coli* in some animals and samples of raw meats [33].

The antibiotic and the resistant antibiotic bacteria are occurred from the same origin these can be often seen together. Waste water or sewages, aquatic culture, agricultural runoff, animal manures these contain bacteria's which are resistant to antibiotics[34].Due to antibiotics injudicious usage, water treatments are not much efficient in removing antibiotic concentrations. To obtain the concentration of antibiotics present in a particular region drinking water, sewages, soils and other sources of water can be analysed.



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VARIOUS MECHANISM INVOLVED IN THE RESISTANCE OF ANTIBIOTICS

Nature's natural selection process, molecular structure changes in the bacteria, efflux mechanism, transferring resistant genes, multiresistant gene and forming non-resistant bacteria [35] are the some of the methods involved in antibiotic resistance.

Antibiotics like Cephalosporin's, Macrolides, Aminoglycosides, Tetracycline etc., disinfectants, cosmetics, preservatives added in the food, detergents can enter our environment and generate multi-resistance to these agents and multi-resistant genes present in the organisms can be transferred and cause non-resistant bacteria[36]. Manufacturers of antibiotics, pharmacists, physicians, farmers, patient and patient parties or those who are using or handling antibiotic medications are responsible for the antibiotic resistance.

Various mitigation strategies such as sewage treatment or waste water treatment, activated carbon treatment, membrane filtration and ozonation for removing bacteria's and antibiotics, UV disinfection and heat treatment are more beneficial in eradicating viable bacteria's. Prevention is always better than a major disaster, like superbugs obtained from antibiotic resistance. Hence, in future various methods like reducing antibiotics overall release, judicious use of antibiotics in hospitals, legal actions for OTC dispensing of antibiotics, special regulations for antibiotics production and discarding of waste water from manufacturing companies and agriculture and veterinary uses [36].

Left over medications can result in treatment delays, exacerbation of diseases, antibiotic resistance, disabilities, increased hospitalisations, increased expenditure for the treatment and death [37]. Various reasons behind the medication accumulations, are misuse of medications, poor compliance to the therapy, therapy changes like addition of new medication/ replacement of a medication, complex regimen, poly-pharmacy, dementia, death of patient [38].

ROLE OF PHARMACIST IN IMPROVING ANTIBIOTICS USE

To assist physicians in prescribing the most appropriate antimicrobial agent and insist them to prescribe antibiotics in generic names.

To counsel the patients or patient parties regarding antibiotic administration, its indication, route, frequency, duration, benefits of completing antibiotics and problems associated with antibiotic resistance this will improve patient compliance in taking antibiotics.

To create awareness regarding, formulary list/antibiotic list among healthcare professionals and thereby, promoting hospital formulary antibiotics for prescribing and dispensing.

Promoting and implementing antibiotic stewardship programme in each hospitals.

Identify the counterfeit medications and avoiding these medications, being prescribed by the physician.

Do not dispense antibiotics by OTC or without prescription.
Create public awareness regarding benefits of safe disposal of antibiotics.

4. CONCLUSION

Antibiotic therapy eradicates the infectious microorganisms; even it affects the normal protective flora in the body. Hence, antibiotics can be called as endangered species, which are facing extinction due to resistance. Evidence based therapy is better than empirical therapy, which enhances individual patient care there by it may reduce the cost of the therapy, reduce the length of stay in hospital, decreases antibiotic resistance. Clinical inspections regularly in dairy animals, sensitivity testing before antibiotic administration, controlling of antibiotic sale by OTC, implementation of antibiotic stewardship in healthcare sectors like hospitals, community care can improve antibiotics use in judicious manner.

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