

ROLE OF ALTERNATIVE THERAPIES IN MITIGATING ANTIMICROBIAL RESISTANCE

Abstract

The successful use of any therapeutic agent is compromised by the potential development of tolerance or resistance to that compound from the time it is first employed. This is true for agents used in the treatment of bacterial, fungal, parasitic and viral infections and for treatment of other chronic diseases. In the specific case of antimicrobial agents, the complexity of the processes that contribute to emergence and dissemination of resistance cannot be overemphasized and the lack of basic knowledge on these topics is one of the primary reasons that there has been so little significant achievement in the effective prevention and control of resistance development (Cushnie and Lamb, 2005).

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I. INTRODUCTION

Antibiotics have revolutionized medicine in many aspects and countless lives have been saved; their discovery was a turning point in human history. Regrettably, the use of these wonder drugs has been accompanied by the rapid appearance of resistant strains.

Many of the bacterial pathogens associated with epidemics of human disease have evolved into multidrug-resistant (MDR) forms subsequent to antibiotic use. For example, MDR *M. tuberculosis* is a major pathogen found in both developing and industrialized nations and became the 20th-century version of an old pathogen. Other serious infections include nosocomial (hospital-linked) infections with *Acinetobacter baumannii*, *Burkholderia cepacia*, *Campylobacter jejuni*, *Citrobacter freundii*, *Clostridium difficile*, *Enterobacter* spp., *Enterococcus faecium*, *Enterococcus faecalis*, *Escherichia coli*, *Haemophilus influenzae*, *Klebsiella pneumoniae*, *Proteus mirabilis*, *Pseudomonas aeruginosa*, *Salmonella* spp., *Serratia* spp., *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Stenotrophomonas maltophilia*, and *Streptococcus pneumoniae*. This led to the emergence of the term “superbug” which refers to microbes with enhanced morbidity and mortality due to multiple mutations endowing high levels of resistance to the antibiotic classes specifically recommended for their treatment; the therapeutic options for these microbes are reduced and periods of hospital care are extended and more costly.

Many strategies for avoiding, inhibiting or bypassing resistance mechanisms in pathogens have been attempted. The most notable successes in such endeavours have been with the β -lactam antibiotics. Clavulanic acid and related compounds are potent inhibitors of β -lactamase enzymes and are frequently used in combination with the β -lactam antibiotics. These combinations have been highly effective, but bacteria have found a way to outsmart us: a number of β -lactamases that are refractory to inhibition by clavulanate have appeared. To date, research to extend this approach to other classes of antibiotics has not been successful (McArthur *et al.*, 2013).

II. DRUG RESISTANCE IN FOOD BORNE PATHOGENS

The animals carry bacteria in their intestines and giving antibiotics will kill many bacteria, but resistant bacteria survive exposure to the antibiotic and continue to multiply in the body, potentially causing more harm and spreading to other animals or people. During slaughtering and processing of food animals, the resistant bacteria not only contaminate the meat or other animal products but also enter into environment. There are several direct routes by which people can get antibiotic-resistant bacteria that develop in industrial food animal production:

1. Improper handling or consuming inadequately cooked contaminated meat.
2. Contact with infected farm workers / meat processors, or perhaps their families.
3. Drinking contaminated surface or ground water and eating contaminated crops.
4. Contacting air that is vented from concentrated animal housing or is released during animal transport.

III. PREVENTION AND CONTROL

1. Drug licensing and banning or restricting the use of certain drugs.
2. Improving hygiene and animal health through immunization, safe food preparation, hand washing and using antibiotics as directed and only when necessary. In addition, preventing infections also prevents the spread of resistant bacteria.
3. Implementing microbial criteria for certain types of resistant pathogens for use in the control of trade of both food animals and food.
4. Improving antibiotic prescribing/stewardship: Perhaps the single most important action needed to greatly slow down the development and spread of antibiotic-resistant infections is to change the way antibiotics are used. Up to half of antibiotic use in humans and much of antibiotic use in animals is unnecessary and inappropriate and makes everyone less safe. Stopping even some of the inappropriate and unnecessary use of antibiotics in people and animals would help greatly in slowing down the spread of resistant bacteria. This commitment to always use antibiotics appropriately and safely—only when they are needed to treat disease and to choose the right antibiotics and to administer them in the right way in every case is very important to prevent resistance.
5. Tracking of gathered data on antibiotic-resistant infections: Includes causes of infections and whether there are particular reasons (risk factors) that caused some people to get a resistant infection. With that information, experts can develop specific strategies to prevent those infections and prevent the resistant bacteria from spreading.
6. Developing new drugs and diagnostic tests: As antibiotic resistance occurs as part of a natural process in which bacteria evolve, it can be slowed but not stopped. Therefore, we will always need new antibiotics to keep up with resistant bacteria as well as new diagnostic tests to track the development of resistance.

IV. FACTORS WHICH PROMOTE ANTIMICROBIAL RESISTANCE

1. Exposure to sub-optimal/inappropriate levels of antimicrobial
 - Prescription not taken correctly
 - Antibiotics sold without medical supervision
 - Lack of quality control in manufacture or outdated antimicrobial
 - Inadequate surveillance or defective susceptibility assays
 - Widespread use of antibiotics in animal husbandry and agriculture and as medicated cleansing products
2. Exposure to microbes carrying resistance genes

V. ALTERNATIVES TO ANTIMICROBIALS

There are increasing problems with effective current antimicrobial therapy and a search is on for viable non-antibiotic alternative to treat bacterial infections. Many alternatives for antimicrobial therapy are nowadays in use, on which scientists are working. Some of these are as follows:

1. **Bacteriophage Therapy:** The bacteriophages appear to be ubiquitous and most of these phages have double-stranded DNA. Bacteriophages undergo two possible life cycles.

These are the lytic (or virulent) and lysogenic. Lytic phages multiply within bacteria and kill the host cell at the end of the growth cycle.

Phage therapy, one of the most accepted phage applications, is quite attractive for the number of reasons. In the present scenario, antibiotics are not as profitable as other drugs (*e.g.*, drugs to treat diabetes, asthma, or gastro-oesophageal reflux) and development of new antibiotics is no longer accepted by corporate world. It would be wise to reconsider and rediscover phage therapy because bacteriophages are very specific to their host which in turn minimizes the chance of secondary infections. Also, bacteriophage replicate at the site of infection where they are mostly needed to lyse the pathogens. No side effects have been reported during or after phage application.

2. Cow Urine Therapy: From time immemorial, Ayurveda has understood the value of a cow. It is a great producer of milk and the dairy products, having many properties. Yogurt, butter milk, organic milk, ghee and other milk by-products have a high nutritional value by providing calcium and protein to the human body tissues and cells. Ghee and cow dung fed in fire ceremonies popularly known as Yagna, has been found to help in purification of air. Ayurveda has a firm belief with proper facts to prove that some diseases cannot be totally cured by medicines alone.

- **Biochemical Importance of Cow Urine:** Cow urine is a liquid discharge consisting of non toxic waste material from the cow body. The main constituents of cow urine are water: 95%, followed by urea: 2.5% and the rest 2.5% is a mixture of different minerals, salts, hormones and enzymes. Antimicrobial and germicidal properties of cow urine are due to the presence of urea, creatinine, aurum hydroxyide, carbolic acid, phenols and salts of calcium and manganese. Its anti carcinogenic effect is due to uric acid, which has antioxidant property. Aurum hydroxide improves immunity and allantoin promotes wound healing. Hence, administration of a dosage of cow urine helps in regulating an appropriate balance of the above mentioned substances, thus curing incurable diseases. Cow is hence considered a live dispensary; a store house of medicines.
- **Mechanism of Action of Cow Urine:** The prominent antimicrobial property of cow urine is due to its volatile and non-volatile components like urea, creatinine, aurum hydroxide, phenol, carboxylic acid and salts of calcium and manganese. This germicidal property is even more enhanced due to the presence of different amino acids and urinary peptides which are instrumental in increasing the bacterial cell wall and surface hydrophobicity. It has also been observed that fresh cow urine is more effective as an antimicrobial agent than its distillate due to the presence of higher concentration of phenol. The early morning voided cow urine has been observed to be more sterile and has more micro and macro nutrients, enzymes and other components, which render it to be most effective.

Patents: Three U.S. Patents have been registered on Gomutra Ark (researched and authorized by U.S. Government).U. S. Patent No.1-6410059,dated June 25,2002.U.S.Patent No.2- 6896907,dated May 24,2005 and U. S. Patent No.3-7235262,dated June 26,2007 (Khanuja *et al.*, 2002).

- 3. Herbal Drugs:** Herbs have been used for many years as food additives and traditional medicine against a number of infectious agents. The most commonly used herbs that possess antimicrobial properties are garlic, black cumin, cloves, cinnamon, thyme, mustard etc. Herbs are potent antimicrobials and can replace synthetic preservatives like ButylatedHydroxyanisole (BHA) and ButylatedHydroxytoluene (BHT) used in the food industry. According to WHO, herbs can be the best source to obtain a variety of drugs. It is observed that there are complex interactions between different functional groups of herbal drugs like phenols, aldehydes, ketones, alcohols etc. It is a fact that the herbs containing cinnamaldehyde, citral, carvacrol, eugenol or thymol (aldehyde or phenol as functional groups) possess the higher antibacterial activity in comparison to other herbs/essential plant oils (Inouye *et al.*, 2001; Nostro *et al.*, 2002).
- 4. Antimicrobial Peptides:** Plants, animals and fungi have vastly different immune systems, but all make peptides — small proteins — that destroy bacteria. Peptides from creatures such as amphibians and reptiles, which are unusually resistant to infection, could yield new therapeutics. Peptides with antibacterial activity have been isolated from frogs, alligators and cobras, among others, and some seem to be effective in epithelial cell cultures and at healing wounds in mice. A vast number of antimicrobial peptides (AMPs) are considered a major source of potential novel agents (e.g. Magainins, Cathelicidins, Lactoferrins and Defensins) particularly against strains that exhibit multidrug resistances. Particular interest has been shown in cationic AMPs against Gram-negative bacteria since their mechanism of action is biophysical (i.e. it disrupts the cell membrane) and is considered resistance proof, as there is no identified evasion/adaptation method for the target bacteria. This gives antimicrobial peptides a superior property as they target the Achilles heel of the unique but essential feature of microbial cellular membranes. These peptides can be modified to increase their potency, and several are in clinical trials. One, called pexiganan, based on a peptide from frog skin, is now in phase III clinical trials to treat diabetic foot ulcers. But synthesizing such molecules can be expensive, a hurdle that scientists must overcome to bring new peptide drugs to market.
- 5. Bacteriocins:** Antimicrobial peptides (AMPs) are increasingly of interest as alternatives to classic antibiotics. However, because many Antimicrobial peptides are toxic to mammalian cells, they are not good candidates for therapies. A subcategory of Antimicrobial peptides that lacks this drawback is the bacteriocins. These compounds are commonly described as small ribosomally synthesized peptides that are secreted by bacteria and inhibit the growth of closely related species. Bacteriocins function by inserting themselves into the plasma membrane of target bacteria, forming pores and causing lysis. Bacteriocin production has been found throughout the major lineages of bacteria; by some estimates up to 99% of all bacteria produce at least one bacteriocin. Consequently, there is vast diversity among these compounds, which potentially could be exploited for therapeutic purposes. Many commensal bacteria endogenously produce bacteriocins, and thus exploiting or modulating such bacteriocins may be promising. For example, one group of commensal microbes, the lactic acid bacteria (LAB), produce bacteriocin nisin A, which, owing to its bacteriocidal activity, is currently used in over 50 countries as a food preservative. In addition to their food-safety applications, bacteriocins can be used effectively in treatment of human pathogens, including multi drug resistant pathogens. For example, a bacteriocin produced by *Enterococcus faecium* is effective against vancomycin-resistant *Enterococcus* (VRE) strains (species not reported).

- 6. Endophytes:** Endophyte, by definition, is one which resides in the tissues beneath the epidermal cell layers and causes no apparent harm to the host (Stone *et al.*, 2000). Endophytes have a wide range of antimicrobial producing strains, which are the important potential sources of antimicrobial substances (Ryan *et al.*, 2008). Studies have shown that, nearly 300,000 plant species that exist on the earth, each individual plant is the host to one or more endophytes, the population of a given endophytic species varies from several to a few hundreds strains (Strobel and Daisy, 2003; Huang *et al.*, 2007). There is a complex relationship between endophytes and their host plants. It is believed that endophytes indirectly benefit plant growth by producing special substances mainly secondary metabolites to prevent the growth or activity of plant pathogens.

VI. STEPS TO COMBAT ANTIMICROBIAL RESISTANCE

1. The implementation of national efforts to prevent antimicrobial resistance should be through a multi-sectorial, national steering committee headed by the senior-most health executives and facilitated through advisory or expert groups.
2. Implement appropriate surveillance mechanisms in the health and veterinary sectors to generate reliable epidemiological information, baseline data, trends on antimicrobial resistance, utilization of antimicrobial agents and impact on the economy and health through designated national and regional reference centre's. Discourage non-therapeutic use of antimicrobial agents in veterinary, agriculture and fishery practices as growth-promoting agents.
3. Develop national standard treatment and infection control guidelines and ensure their application at all levels of health care and veterinary services through training, continuous educational activities, establishment of functional drugs and therapeutic committees and hospital infection control committees in health facilities with the focus on proven cost-effective interventions such as isolation, hand washing.
4. To regulate and promote rational use of medicines and ensure proper patient care at all levels, there is a need to take necessary steps to stop across the counter sale of antibiotics without physicians prescription and ensure uninterrupted access to essential medicines of assured quality at hospital and community. Also, vaccination strategies should be improved to further reduce the burden of infections.
5. Conduct of operational research for better understanding of the technical and behavioral aspects of prevention and control of antimicrobial resistance. Utilize the outcomes of these research studies or interventions in policy and program development improvement in the national context.
6. Constructive interactions with the pharmaceutical industry for ensuring appropriate licensure, promotion and marketing of existing antimicrobials and for encouraging the development of new drugs and vaccines.
7. Educational and awareness program for communities and different categories of health care professionals. Strengthen communicable diseases control program to reduce disease burden and accord priority to the discipline of infectious diseases in medical education and health services.
8. Developing the Swachh Bharat Abhiyan into a cross-cutting programme encouraging espousal of open defaecation free zones, better sanitation and hygiene standards, and awareness of infection prevention at the community level is likely to reduce infection load, thus leading to lesser propensity to consume antibiotics. However, India remains as

one of the nations with a very high proportion of bacterial infections, especially in areas with poor water, sanitation and hygiene conditions.

9. Patients must stop taking antibiotics for self-limiting infections.
10. Doctors have to stop giving unnecessary antibiotic prescriptions. Optimum dose, route of administration and duration of therapy should be prescribed.
11. Patients must follow and complete antibiotic prescriptions.
12. Using the right antibiotic determined by antibiotic sensitivity testing.
13. Stop the use of antibiotics as growth-promoting substances in farm animals.
14. Combination of agents is necessary like β -lactam and Aminoglycosides, Extended spectrum Penicillins and β -lactamase Inhibitors.
15. Adjunctive measures can be undertaken to eradicate infection which includes: vaccination, steroids, drainage of pus, amputation, removal of catheter.
16. Search for new antibiotics. Biotechnology and pharmaceutical companies must constantly research, develop and test new antimicrobials in order to maintain a pool of effective drugs in the market against the rise of resistant bacteria.
17. As policy makers: Control the use of antibiotics through supervision of well-trained veterinarians, prevent the circulation of non-quality products, encourage research on alternative treatments to antibiotics, ensure that appropriate legislation supports Veterinary Services, raise awareness on the responsible and prudent use of antibiotics in animals based on OIE standards.
18. The Agriculture sector should ensure that antibiotics given to animals including food producing and companion animals are only used to control or treat infectious diseases and under veterinary supervision. Vaccinate animals to reduce the need for antibiotics and develop alternatives to the use of antibiotics in plants. Promote and apply good practices at all steps of production and processing of foods from animal and plant sources. Adopt sustainable systems with improved hygiene, biosecurity and stress-free handling of animals. Implement international standards for the responsible use of antibiotics and guidelines, set out by OIE, FAO and WHO.

VII. CONCLUSIONS

The importance and value of antibiotics cannot be overestimated; we are totally dependent on them for the treatment of infectious diseases and they should never be considered mere commodities. Resistance mechanisms are pandemic and create an enormous clinical and financial burden on health care systems worldwide. There are no simple solutions to the problem. Decisive actions that require significant commitment and enforcement are never popular, even if lives can be saved. Fortunately, not all bacterial pathogens are resistant all of the time and many respond to empirical treatment with antimicrobial agents administered in the community. Success is perhaps due to luck rather than to good judgment. Given the many imponderables, the best one can expect is that all physicians and health care centers provide their patients with environments that are resistance-free by taking stricter measures in infection control and antibiotic use. This must be backed up by efforts to prevent dumping of antibiotics into the environment through sewer systems; complete destruction of antibiotics before disposal should be common practice.

There is no perfect antibiotic and once the most appropriate uses of any new compound are identified, it is essential that prescription of the antibiotic be restricted to those

uses. This means that defined “niche” antibiotics should be developed as a class separate from broad-spectrum agents.

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