Acta Scientific Veterinary Sciences (ISSN: 2582-3183)

Volume 4 Issue 5 May 2022

Review Article

A Monograph on Antimicrobial Resistance (AMR) and Alternatives Strategies to Counter AMR

Anilkumar Banothu*

Assistant Professor, Department of Veterinary Pharmacology and Toxicology, College of Veterinary Science, Rajendranagar, Hyderabad

***Corresponding Author:** Anilkumar Banothu, Assistant Professor, Department of Veterinary Pharmacology and Toxicology, College of Veterinary Science, Rajendranagar, Hyderabad.

DOI: 10.31080/ASVS.2022.04.0396

Received: March 29, 2022

Published: April 29, 2022

Abstract

Antimicrobial agents have been used in human beings, livestock and aquatic animals for life saving against the various disease caused by the infectious organisms like bacteria, viruses, parasites, fungus and cancerous cells since Second World War. Over a period of time, many antimicrobial agents have been invented by scientists and at the same time organism also started to develop resistance to the existed antimicrobial agents which happened due to mainly misuse or inappropriate usage of antimicrobial agents. Nontherapeutic usage of antibiotics also leads to the development of superbugs that are resistant to many of the existing antibiotics. Further, mutation of gene within the bacteria and passing the resistant (R) gene through horizontal gene transfer could viable method for the contribution of development of resisntance. In this monograph discussed the genetical and biochemical mechanism of development of resistance by the bacteria and also delineate alternative strategies likes use of phytochemicals, probiotics, biofilm breakers, vaccine, antimicrobial peptide, nano particles, monoclonal antibodies, quarum quencher, anti peristance, lantibiotics, etc., are the possibilities to counter antimicrobial resistance.

Keywords: Monograph; Antimicrobial Resistancel; Alternatives Strategies; AMR

Introduction

Antibiotics are derived from the concept antibiosis which means life against life. Antibiosis concept was given by Luis Pasteur and Joubert in the1877 and antibiotics term was coined from the antibiosis concept by Dr. Selman A. Waksman, soil microbiologist who discovered several actinomycetes derived antibiotics [1]. Antibiotics are chemicals elaborated by living microbes and capable of inhibiting other microbes in very low concentrations. Antibiotic is a chemical substance produced by a *microorganism* that inhibits the growth of or kills other microorganisms [2]. Each antibiotic has different properties like physical, chemical, MOA, antibacterial spectrum Types of antibiotics 1. Antibacterial 2. Antifungal 3. Antiprotozoan 4. Antiviral and are employed in the treatment against disease causing agents of human and animal health. Alexander Fleming invented Penicillin in the year of 1927 while working on *Straphylococcus aureus* culture at St. marry hospital, Landon and paved pathway for the subsequent inventions of other groups of antibiotics like Tetracyclines, Macrolides, Aminoglycosides, Fluoroquinalones etc [3]., Antimicrobial agents are classified according to their mechanism of action as 'Bactericidal agents' which interference the cell wall synthesis (or) DNA synthesis (or) RNA synthesis (or) interfering cell membrane function, and 'Bacteriostatic agents' which are capable of inhibiting growth and multiplication of bacteria by interfering protein synthesis (or) inhibition of metabolic pathways, etc. Meanwhile, bacteria may become resistant to these drugs by antibiotic inactivation, target modification, development of efflux pump and plasmids efflux.

Anti-Microbial Resistance (AMR) in microbes is defined as their unresponsiveness to standard doses of clinically relevant antimicrobial drugs which means that microbes overpower will antagonize the action of antibiotics by an earlier sensitive organism. Consequences of AMR may lead to the development of multi-drug-resistant (MDR) strain of organism (more challenging to treat), extensively drug-resistant (XDR) strain (critical concern) and pan-resistant (PDR) organisms which are practically impossible to treat with standard therapies [4]. In this review, discussed about genetic and biochemical mecha-

nism of resistance by the bacterium towards conventional antibiotics and also emphasized novel alternatives therapy to combat the emergence of resistance by the microorganism.

General mechanism of resistance by the bacteria: 2 types of bacterial resistance

- Natural resistance: the inherent capacity of an organism or genetically resistant to an antimicrobial agent (AMA) and the kind of resistance is called natural. The reason/ factor for the natural resistance is lack of penetration of the drug in to the cell, absence of metabolic pathways or target site affected by the drug and rapid inactivation of the drug in the bacterial cell. Ex: Penicillins are resistant to G-ve organisms.

- Acquired resistance: it happened when the use of AMA for over a period of time and unresponsiveness use of AMA, Organism develops resistances that are previously sensitized to the particular type of AMA. Continuous usage of single antibiotics may lead to sensitivity in 95% of organism and the remaining 5% of microbes will develop to resistance.

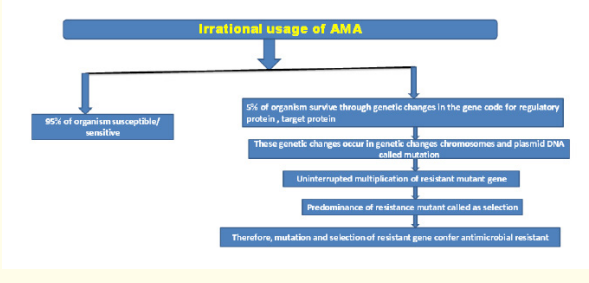

Figure a

Genetical mechanism of acquired remittance: Acquire resistance may develop by mutation (within bacteria) or gene transfer (within bacteria)

- **Mutation**: In the process of mutation stable and heritable changes in the gene of individual micro-organism. Mutation occurs due to insertion, deletion or substitution of one or more nucleotide in the genome as result genetic changes take place in chromosomes or plasmids and these types of genes are called transposons or jumping gene. These genetic changes occur in the genes that are encoded for targets or transporter proteins or drug activating enzymes or changes in the regulatory genes or promoters. Genetic changes may occur at a single gene or multiple genes and genetic changes are taked by different modes like transposons or gene cassette.

    - Transposons/Jumping gene: These transposons are moveable stretches of DNA that moves from plasmid to chromosome, chromosomes to chromosomes or chromosomes to plasmid and this process is called transposition, Copy/paste or cut/paste of one or 2 genes within the bacterium.

    - Gene cassette/ integrons: multi drug gene resistance possible by this ways, gene attached to gene cassette at a particular recognition site in the genome, multigene packed together to form multi cassette array, mutli cassette array integrated with integrase/ Recombinase enzyme called as integron which is also mobile large DNA unit that moves freely from plasmid to chromosomes, wise versa

- **Gene transfer**: Resistance gene (R factor gene) gets transferred from one bacteria to another organism.

    - Vertical gene transfer: R factor gene transfer from parents to F1 generation

    - Horizontal gene transfer: 3 types

    - Conjugation: R gene gets transferred by R Plasmid

    - Transduction: R gene gets transferred by Bacteriophage

    - Transformation: R gene gets transferred by Nacked DNA

Conjugation: R genes get transferred from one bacterium to another bacterium by the formation of sex pili or bridge called conjugation. This is the most important method of R gene get transfer mostly bacteria get resistant through this method). R gene gets transferred from donor to recipient bacteria [5]. There are 2 sets of genes get transferred named as set1gene called as Resistant Determinant Factor (RDF) which is responsible to resistant gene & set

2 genes are called as Resistant Transfer Factor (RTF) required for formation of sex pili. 2 types of conjugation generally seen 1. Compete genome transfer in which complete genome of the plasmid gets transferred from donor to recipient 2. Partial genome transfer in which one or two gene gets transferred from one bacterium to another bacterium. Example *Haemophilus*, develop resistance to the Penicillin, Non pathogenic organism to pathogenic organism, G-ve to G+ve organism

Transduction

R genes get transferred from one bacterium to another bacteria by bacteriophage intervention [5]. The virus does not have its own metabolic machinery for the viral replication process, it depends up enzyme on other bacteria for their replication. During the replication process bacterial R genes get incorporated into the viral genome and provirus contain R gene. Subsequent replication process the R gene containing virus affecting other normal bacterium and transfer R gene. Ex: *Streptococcus aureus* and *streptococcus* develop resistance to Penicillin.

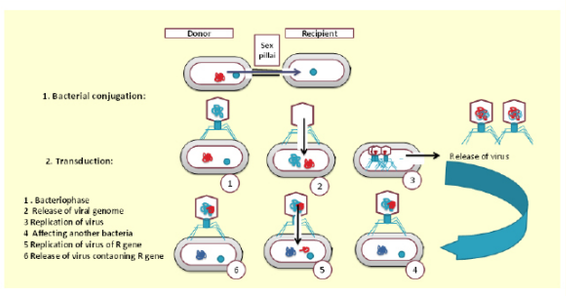

Figure b

Transformation

R genes get transferred from one bacterium to other bacteria by Naked DNA from the environment surrounding [5]. Some bacteria capability to excrete their DNA in to the environment and some bacterial cell lyses. Some species of bacteria take these genes in their genome by cross over/ recombination process. Ex: some trains of *Pneumococci,* and *Neisseria.*

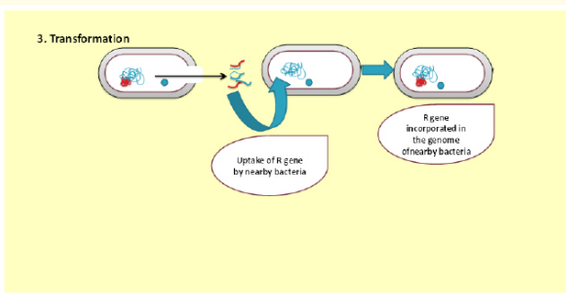

Figure c

Biochemical mechanism of resistance

Mutant genes also get transferred by following

- Reduce the entry of AMA into the bacterium: generally many antibiotics entry into the bacterium cell by aquaporin and ion channel, mutation of the gene that encodes for aquaporin and transporter protein leads reduce the entry of antibiotics in the bacterium cell [6]. Example Aminoglycosides entry into G-ve bacterial cell. Induce development of efflux pump on the cell membrane, tetracycline get resistance by the development of efflux pump

- Increased inactivation of antibiotics in the bacterial cell by the production of metabolizing enzymes Ex: Beta-Lactum antibiotics by Beta lactamases, Chloramphenicol by chloramphenicol acetyl transferase, AGs by Adenylases, Phosphorylase, acetalses [7].

- Alteration of binding sites and targets. Alteration of the binding site of 30s ribosome Ex. AGs, Tetracyclines. Alteration of the binding site of 50s ribosome Ex. Macrolides, chloramphenicol, oxazolidones, clindamycin. Alteration of target enzymes Ex. DNA Gyrase by the FQ, Transcriptase by Rifamycin [8].

- Alteration in the metabolic pathways: Bacteria synthesizes folic acid through their own metabolic pathway eventually folic acid utilizes for the synthesis of purine and pyrimidines (DNA) by using the two enzymes Dihydropteroate synthase and Dihydrofolate reductase (DHFR) and sulfa drugs are acts by inhibiting these enzymes at 2 step sequence. Ex. Alteration of enzymes Dehydropteroate synthase thereby sulfonamides could not act and DHRF by Trimethoprim [9].

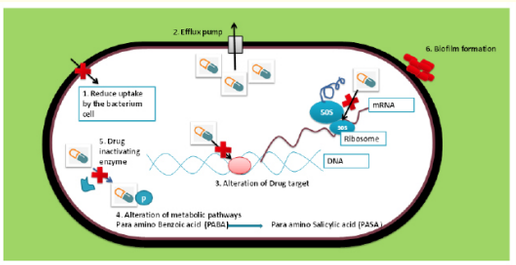

Figure d: Showing biochemical mechanism of drug resistance in the bacterium.

How to overcome the resistance/Steps to avoid resistance

- Always use definitive therapy/ rational therapy not used as empirical therapy.

- Avoid the use of antibiotics as indiscriminately/ irrationally
- Antibiotics should be given prescribed or adequate therapy
- Sometimes need to follow poly antibiotic therapy in case of multiple infections
- Avoid usage of antibiotics as growth promoters in the feed
- Always follows the time course of antibiotics
- Specific diagnosis techniques employed for isolation and identification of the organism and treatment accordingly

Use of antibiotics in livestock and poultry

Usage of antibiotics in livestock farming has largely contributed to good health and an increase in productivity, simultaneously; irrational usage has played a significant role in evolution of resistant strains. Dairy farming and the poultry industry are involved in the surplus use of antibiotics as prophylactic and growth promoting agents and when it was added to animal feed it turned out to be an excellent growth promoter as well [10]. But bacteria defend themselves by developing resistance. A rapid spread of bacterial resistance to antimicrobial agents may limit the future progress of medicine and will pace a global problem. There are several factors involved in the development of AMR and are indiscriminate use of antibiotics, selection of inappropriate antibiotics, lack of laboratory testing facilities, inadequate duration of therapy, environmental antibiotic selective pressure and diversified resistant gene get selected which are expected to result in a significant acceleration of the rate of microbial evolution.

AMR global issue: Increasing globalization it has possible to the marketing of agricultural products, exporting and importing of livestock and its products, human travel across the country thus facilitating the rapid spread of R gene thus making challenges to counter the spread of R gene. Example emergence of a plasmid-mediated resistance gene (mcr-1) to colistin, has been identified in people and pigs in China [11] followed by Europe and Canada to the USA [12].

One health: both animal and human beings are treated with the same kind of conventional antibiotics which could contribute to driving the transmission of R gene between animals and human being through the environment. Therefore, the One Health approach came into existence, which envisages the collaborative effort of multiple disciplines - working locally, nationally, and globally - to attain optimal health for people, animals and our environment [13] and also recognizes that the health of people is connected to the health of animals and the environment.

AMR has now emerged as a global public health issue and threatened all kinds of creatures across the globe in terms of environment, food production, poverty and health security. In the context of 'One Health', the consequences of the spread of AMR bacteria from food animals may have a profound impact on both animal health and public health. Considering the global health impact of AMR bacteria and the need for new antibiotics, new strategies are being implemented to protect and treat MDR, XDR, and PDR infections as even so-called 'antibiotics of last resort' are becoming ineffective in clinical settings.

Alternative strategies

To overcome this AMR problem, there is a dire need for alternative methods for alleviating microbial infections rather than drugs. Efficient and laudable supervision programs at the interdisciplinary level can overview to better comprehension and reduce the occurrence of the emergence of resistance

- **Combination therapies:** Combination prescribing two or more antimicrobial agents simultaneously for the potentiating or synergistic action posing more advantages for the treatment of different ailments. example β-lactam antibiotic combined with an aminoglycoside antibiotic, being widely used for the treatment of various Gram-negative bacterial infections while combination of β Lactamase inhibitors with β lactam resistant strain has offered potentiating activity of β lactam antibiotics example of β lactamase inhibitors (such as clavulanic acid, sulbactum and tazobactam) with β-lactam antibiotics help restore the action of β-lactam antibiotics. antibiotic combination with β-Lactamase inhibitors example β-lactam antibiotic-resistant infections, the combination of β-lactamase inhibitors such as sulbactam, clavulanic acid, and tazobactam [14]. Further, the co administration of antimicrobial agents along with biocides like antiseptic, disinfectants and preservatives have been used for treating pseudomonal infection.

- Use of medicinal plants and phytochemicals: Plants have different metabolites like primary metabolite, important in growth, energy and photosynthesis while secondary metabolites involved in protecting themselves from the hostile environment, pathogens like microorganisms via natural phytochemicals [15,16]. The medically important plant derived substances (PDSs) which are possess antimicrobial action due to the presence of various secondary metabolites like phenolics, organosulphur, terpenes, alkalloids and coumarin and also organosulfur compounds are possing antimicrobial activity by interfering with sulfhydryl group of enzymes, replication of DNA, protein biosynthesis and genesis of ATP in gram positive and gram negative bacteria [17]. Further, alkaloids also interfere with division of the cell, protein formation, and DNA replication in *E. coli* and also inhibit enzyme ATP synthase in *Listeria, Bacillus,* and *Staphylococcus spp*.

- Use of probiotics as an alternative to the development of AMR. The administration of these live microorganisms can confer antibiotics effects by competition at the desirable site [18]. The strength of probiotics in the fight against AMR mainly relies upon competitively inhibiting through selective pressure by the probiotics on virulent organisms.

- Antimicrobial Peptides (AMP) from bacteria and certain insects have been demonstrated antimicrobial activity [19]

- Use of Lantibiotics (Lanthionine containing antibiotic). These are produced by using Gram positive bacteria which can exert antimicrobial activity against themselves. Bacteriocins are a type- A lantibiotic, that are proteinaceous or peptidic toxins produced by the bacterium. These molecules can able to prevent the growth of similar strains of the bacterium or unrelated bacteria but could not prevent the growth or kill the original bacteria due to presence of specific protein that is capable in strong immunity.

- **RNA silencing:** RNA silencing by different strategies for the screening of natural and synthetic RNA silencing and its aptitude to offer new antimicrobial agents [20].

- **Anti-persister drugs:** Anti persister drugs are screened and therapeutically developed against persister cells. The disadvantage of bacterial persistence is to increasing intimidation of resistance while curing the persister cell as they are going to start recolonization and relapse post treatment of antimicrobial agent eventually leading to chronic resistant infections [21]

- The quorum quencher are the agents which are capable of inhibiting quorum sensing of microbes that actually involved bacterial propagation, altering mechanical communication of bacteria, virulence, biofilm formation and adaptation of stress [22]

- **Production of monoclonal antibodies (mAbs):** These are used to treat infections caused by nosocomial bacterial pathogens. Some of mAbs like Obiltoxaximab, Raxibacumab, Bezlotoxumab have been licenced for prevention or clinically to treat certain Gram positive bacteria *Bacillus anthracis* and *Clostridium difficile* [23].

- Screening of drugs molecules against biofilm formation by the bacteria in which antibiotics may not be cross and exerts its effect in the sessile communities. Biolfilm breakers are another alternative to the AMR Dispersion Methods [24]

- **Nanoparticle Based Strategies:** The presence of bulk metals are known to have antibacterial activity against pathogenic bacteria [25]. They are believed to produce antimicrobial activity by oxidative stress, metal ion release, and non-oxidative mechanisms [17,26,27]

- Bacteriophage therapy to individual pathogenic infection: Antimicrobial adjuvants therapy or the application of nanotechnology and plant-based products development of antibiotic stewardship programmes are considered.

- Development of Vaccines in Combating AMR Pathogens: Hepatitis B virus and Bordetella pertussis [28]

- **Gene therapy:** Modern advancement in gene therapy can also be recognized as alternative for the efficacy of gene delivery through vectors [29].

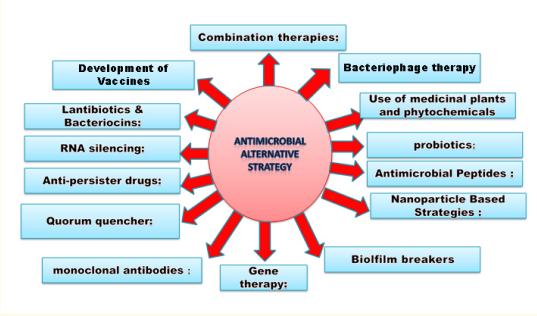

Figure e: Showing various alternative methods to counter AMR.

Conclusion

AMR problem can also be countered by the judicious use of antibiotics in food-producing animals as a non-therapeutic application of antibiotics, their dosage, and withdrawal period need to be re-evaluated and rationally defined. A dairy animal also poses a serious risk of transmission of resistant strains to humans and the environment thereby contaminating the ecosystem. Judicious use of antimicrobial agents in food-producing animals by the veterinarian and supporting staff can mitigate the AMR. Alternative strategies have been clinically tested and few are in the preclinical stage and are clinically evaluated for their therapeutically use to minimize the occurrence of resistance by the organisms.

Bibliography

1. Levy SB. "The antibiotic paradox: how miracle drugs are destroying the miracle". Springer (2013).

2. Etebu E and IJIJAMBR Arikekpar. "Antibiotics: Classification and mechanisms of action with emphasis on molecular perspectives" 4 (2016): 90-101.

3. Cossart. "The new microbiology: From microbiomes to CRISPR". John Wiley and Sons (2020).

4. Murugaiyan J., *et al*. "Progress in Alternative Strategies to Combat Antimicrobial Resistance: Focus on Antibiotics". *Antibiotics (Basel)* 11.2 (2022): 200.

5. Clewell DB. "Bacterial conjugation". Springer Science and Business Media" (2013).

6. Yu L. "Structural and functional characterization of multidrug resistance transporter and regulator". University of Kentucky. *Bull Cancer* (2013).

7. Kashef N and MRJDRU Hamblin. "Can microbial cells develop resistance to oxidative stress in antimicrobial photodynamic inactivation?" *Drug Resistance Updates* 31 (2017): 31-42.

8. Serio AW., *et al*. "Aminoglycoside revival: review of a historically important class of antimicrobials undergoing rejuvenation". *EcoSal Plus* 8.1 (2018).

9. Fernández-Villa D., *et al*. "Folic acid antagonists: antimicrobial and immunomodulating mechanisms and applications". *International Journal of Molecular Sciences* 20.20 (2019): 4996.

10. Sharma C., *et al*. "Antimicrobial resistance: its surveillance, impact, and alternative management strategies in dairy animals". *Frontiers in Veterinary Science* 4 (2018): 237.

11. Liu YY., *et al*. "Emergence of plasmid-mediated colistin resistance mechanism MCR-1 in animals and human beings in China: a microbiological and molecular biological study". *The Lancet Infectious Diseases* 16.2 (2016): 161-168.

12. McGann P., *et al*. "Escherichia coli harboring mcr-1 and bla CTX-M on a novel IncF plasmid: first report of mcr-1 in the United States". *Antimicrobial Agents and Chemotherapy* 60.7 (2016): 4420-4421.

13. Robinson TP., *et al*. "Antibiotic resistance is the quintessential One Health issue". *Transactions of the Royal Society of Tropical Medicine and Hygiene* 110.7 (2016): 377-380.

14. Laure NN and JJP Ahn. "Antibiofilm Activity of β-Lactam/β-Lactamase Inhibitor Combination against Multidrug-Resistant *Salmonella Typhimurium*". *Pathogens* 11.3 (2022): 349.

15. Allawadhi P., *et al*. "Decorin as a possible strategy for the amelioration of COVID-19". *Medical Hypotheses* 152 (2021): 110612.

16. Priyanka G., *et al*. "Adaptogenic and immunomodulatory activity of Ashwagandha root extract: an experimental study in an Equine model". *Frontiers in Veterinary Science* (2020): 700.

17. Allawadhi P., *et al*. "Potential of electric stimulation for the management of COVID-19". *Elsevier Public Health Emergency Collection* 144 (2020): 110259.

18. Mounika B., *et al*. "Effect of probiotic formulation containing *Bacillus spp*. on diarrhoea in dogs". *TPI International Journal* (2019).

19. Singh V., *et al*. "Emerging Role of PD-1/PD-L1 Inhibitors in Chronic Liver Diseases". *Frontiers in Pharmacology* 12 (2021): 790963-790963.

20. Mwaka HS., *et al*. "First Evidence of Feeding-Induced RNAi in Banana Weevil via Exogenous Application of dsRNA". *Insects* 13.1 (2021): 40.

21. Khurana I., *et al*. "Can bilirubin nanomedicine become a hope for the management of COVID-19?" *Medical Hypotheses* 149 (2021): 110534.

22. Ghosh S., *et al*. "Phytocompound Mediated Blockage of Quorum Sensing Cascade in ESKAPE Pathogens". *Antibiotics (Basel)* 11.1 (2022): 61.

23. Raj GM., *et al*. "Monoclonal antibodies against infectious microbes: so long and too little!" *Infectious Disorders Drug Targets* 21.1 (2021): 4-27.

24. Reza A., *et al*. "Effectiveness of efflux pump inhibitors as biofilm disruptors and resistance breakers in gram-negative (ESKAPEE) bacteria". *Antibiotics (Basel)* 8.4 (2019): 229.

25. Khurana A., *et al*. "Role of nanotechnology behind the success of mRNA vaccines for COVID-19". *Nanotoday* 38 (2021): 101142.

26. Allawadhi P., *et al*. "Silver nanoparticle based multifunctional approach for combating COVID-19". *Sensors International* 2 (2021): 100101.

27. Allawadhi P., *et al*. "Biomedical applications of polysaccharide nanoparticles for chronic inflammatory disorders: Focus on rheumatoid arthritis, diabetes and organ fibrosis". *Carbohydrate Polymers* (2021): 118923.

28. Micoli F., *et al*. "The role of vaccines in combatting antimicrobi-