International Journal of Microbiology Research
ISSN: 0975-5276 & E-ISSN: 0975-9174, Volume 11, Issue 7, 2019, pp.-1676-1679.
Available online at https://www.bioinfopublication.org/jouarchive.php?opt=&jouid=BPJ0000234

Review Article

ANTIMICROBIAL RESISTANCE AND ALTERNATIVE OPTIONS

AKHOON Z.A.*[1], MALIK H.U.[1], SHAHEEN M.[1] AND AKHOON A.B.[2]

[1]Division of Clinical Veterinary Medicine, Faculty of Veterinary Sciences and Animal Husbandry, Shuhama, Sher-e-Kashmir University of Agricultural Sciences & Technology of Kashmir, Shalimar, 190019, Jammu and Kashmir, India
[2]University of Kashmir, Srinagar, 190006, Jammu and Kashmir, India
*Corresponding Author: Email - drzubair7866@gmail.com

Received: July 02, 2019; Revised: July 24, 2019; Accepted: July 26, 2019; Published: July 30, 2019

Abstract- Study of the bacterial pathogens associated with epidemics of human disease have evolved into multidrug resistant (MDR) forms subsequent to antibiotic use. There are many important factors contributing to the indiscriminate use of antimicrobials are knowledge, economic incentives and regulatory environment. Some evidence that CAM prevention and treatment strategies can lead to the prescription and consumption of fewer antibiotics. Due to rise in MDR bacteria metal complexation serves as better alternative as it prevents drug resistance and decreases necessary doses.

Keywords- *Antimicrobial Resistance, Drug Resistance, Superbugs and Super resistance*

Citation: Akhoon Z.A., *et al*., (2019) Antimicrobial Resistance and Alternative Options. International Journal of Microbiology Research, ISSN: 0975-5276 & E-ISSN: 0975-9174, Volume 11, Issue 7, pp.-1676-1679.

Academic Editor / Reviewer: Dr Fakir Mohan Sahu, Avinash Sharma

Introduction

Antimicrobials have revolutionized medicine in many aspects and countless lives have been saved. Regrettably the use of these wonder drugs has been accompanied by the rapid appearance of resistance strains. Life is in trouble. Superbugs are spreading fast; more patients are dying of superbug infections each year (with superbugs predicted to be a bigger killer than cancer by 2050) and the developmental pipeline of new antibiotics is worryingly dry. A recent database lists the existence of more than 20,000 potential resistance genes (r genes) of nearly 400 different types predicted from available bacterial genome sequences [1].

Superbugs and Super resistance

Many of the bacterial pathogens associated with epidemics of human disease have evolved into multidrug resistant (MDR) forms subsequent to antibiotic use. *E.g*., MDR M. tuberculosis is a major pathogen and became the 20th century version of an old pathogen. Other serious infections include noscomial infections with *Acinetobacter baumanni, Campylobacter jejuni, C. difficile, Enterococcus faecium, E.coli, K.pneumoniae, Proteus mirabilis, P.aeuruginosa, Salmonella* spp., Stap. *Aureus, Streptococcus pneumoniae etc.*

Superbug – the so-called NDM-1

Multi drug-resistant pathogens exist in India as they do in different forms globally including the western world [2]. The war between drugs and bugs has been on since the time of Alexander Fleming [3]. NDM-1 shares very little identity with other metallo beta-lactamases (MBLs). With a molecular mass of 28kD, NDM-1 possesses unique residues near the active site, with an additional insert between positions 162 and 166, not present in other MBLs.

Development of Drug Resistance

During the growth of microorganisms, they adapt to their environment. If anything stops from growing and spreading them, they evolve new mechanisms to resist antimicrobials by changing their genetic structure.

Bacterial resistance to antimicrobial agent may be due to failure of the drug to reach target or the drug may be inactivated by bacterial enzymes or the target site. The failure of the drug to reach the target site may be due to impermeability of the bacterial cell membrane that will prevent the influx of the drug. Some bacteria are deficient in these channels and hence resistant. Sometimes when exposed to an antibiotic, bacteria can down regulate these porins, or mutate them to reduce their ability to transport the antibiotic into the bacteria. Once the antibiotic has successfully navigated into the bacteria, it may sometimes face bacterial efflux pumps, that eject the xenobiotics back outside the cell. Exposure of the bacteria to an antibiotic can also result in upregulation of these efflux pumps to increase the rate of ejection. To be effective at the target, more antibiotic is needed which dictates the need for a high dose to create sufficient exposure levels. Mutation is stable and heritable genetic change that occurs spontaneously and randomly among microbes not induced by antimicrobial agents. Conjugation occurs through sexual contact by formation of a bridge or sex pilus. Common in G-ve bacilli. Transduction is transfer of gene carrying resistance through the agency of a bacteriophage. Transformation occurs when resistant bacteria release resistance carrying DNA into the medium and this may be imbibed by another sensitive organism. A number of resistant genes have been associated with large transferable extra chromosomal DNA element called plasmid which may be DNA mobile elements such as transposomes responsible for rapid development of resistance. Resistance once acquired by way of the above mechanisms become prevalent due to selection pressure of a widely used antimicrobial agent. Many antibiotic resistance gene resides on plasmids, facilitating their transfer [2-5].

Staphylococcus aureus

One of the major resistant pathogens. Major causative agent for bovine mastitis. One of the earlier bacteria in penicillin resistance was found in 1947. Methicillin was then the antibiotic of choice but MRSA was first detected in UK in 1961. This left Vancomycin as only choice however, VRSA appeared in US in 2002. Others are *Streptococcus pyogenes, Psuedomonas aeruginosa, Salmonella* spp., *E. coli.*

Some Factors Increasing the Spread of Resistance and consequences

Several important factors contributing to the indiscriminate use of antimicrobials are knowledge, economic incentives and regulatory environment. Belief that new and expensive drugs are more efficacious leading to resistance against both new and old. Owner's compliance *i.e*., may forget to give medication, interrupt the treatment when he feels his animal better, unable to complete the full course. All these factors create an ideal environment for microbes to develop resistance. Once an antimicrobial is recognized as resistant, the clinician will switch over to another antimicrobial agent posing financial burden on farmers. Moreover, it increases the duration of treatment thereby reducing the productivity of animal.

Use of Antimicrobials in Veterinary Medicine

Antimicrobials are used in animals to treat and prevent bacterial infection and to improve production efficiency in food animals. In veterinary practice due to lack of facilities mostly empirical therapy is practiced. Extensive use of antimicrobials in veterinary practice contributing much to the development of resistance in human beings by way of consumption of meat, milk and animal products. Moreover, use of antibiotic growth promoters (AMGP) in feed is a usual practice.

Augmentation of Antibiotic Therapy

In addition to antibiotic alternatives, the use of antibiotic adjuvants is one strategy to preserve or enhance the current antibiotic repertoire. Adjuvants include other antibiotics, synergistic non antibiotics and molecules that are inhibitors of resistance genes [6]. There is little confidence that generation of new antibiotics will keep us with the demand from emerging multidrug resistant pathogens because few antibiotics are in development [7]. To tackle with poor penetration due to highly effective bacterial membranes and efflux pumps, researchers have investigated methods to increase the internal concentration of antibiotics through potentiation. Potentiation involves manipulating another typically non essential part of the bacteria to make the organism more sensitive to the antibiotics. An example of potentiation includes efflux pump inhibitors. Efflux pump proteins in the bacterial membrane pump antibiotics out of the cell, rendering them ineffective. One efflux inhibitor, thioridazine, is an approved antiphyschotic drug that has shown effect to treat multi drug resistant Mycobacterium tuberculosis in mice and humans [8]. In a different approach researcher are investigating methods to increase influx by taking advantage of membrane transporters. A popular target for many years is iron uptake from host using siderophore iron transporter as scientists are now trying to add iron binding siderphore mimetic groups to antibiotics(*e.g*. Catechol).

Some Possible Alternatives to Antimicrobials

Some alternatives include management practices, quarantine and biosecurity measures, genetic selection to increase disease resistance, modulating the gut and pulmonary microbiota, vector control, use of probiotics, vaccines, bacteriocins, bacteriophages, predatory bacteria, reactive oxygen technology *etc*. Unlike antibiotics, such alternatives can be targeted to specific bacteria, which is often desirable so as to avoid selecting for resistance of non targeted bacteria. Some of the possible alternatives to antimicrobials are briefly discussed as follows:

Modulating the Gut Microbiota

The mammalian gut microbiota consisting 1010-1012 of bacterial cells per gram of gut contents with more than 1000 species play an important role in human and animal health [9]. The gut microbiota functions as a 'microbial organ' that promotes animal health by modulating the immune system, improves nutrient utilization and excludes pathogens [10]. Altered diversity of gut microbiota can lead to various consequences, including irritable bowel disorder and infection by intestinal pathogens like *Clostridium difficile* [11]. Additional consequences of antibiotic use on gut microbiota include the selection for a reservoir of bacterial antibiotic resistance genes, promotion of horizontal gene transfer between bacterial strains, increased population of enteric bacteria through altered carbohydrate composition and alteration in immune responses in distal organs [12]. Using an alternative to antibiotics that is more specific for a given bacterial target is one way to reduce or eliminate such deleterious side effects on the gut microbiota. The addition of exogenous bacteria to modify the gut microbial community towards health-the use of probiotics has been employed for decades [13]. Rather than applying a single probiotic, complex microbial mixtures are sometimes administered in order to establish or boost the natural bacterial community and to competitively exclude pathogens. This approach has been successfully used in poultry with large scale field trials showing significant decreases in intestinal Salmonella population in birds treated with mixtures of commensal anaerobic bacteria [14]. The lung micobiome: prevent respiratory infections such as ventilator associated pneumonia and *Pseudomonas* in cystic fibrosis. One type of competitive exclusion experiencing a renaissance in human medicine is Faecal Transplant Therapy (FTT), the practice of using faecal material from pathogen free healthy donors to repopulate the microbiota of a recipient. FTT is an ancient practice, used over 2000 years ago in china to treat intestinal illness, and as early as the 17th century in the western world to treat ruminal acidosis in cattle [15]. In the modern era, FTT has been successfully used to treat *C. difficile* infections and is being investigated as a treatment for other intestinal disorders [16]. It is generally accepted that FTT allows patients to reacquire the bacterial diversity that was altered during antibiotic therapy, infection or other causes of dysbiosis [17].

Phage Therapy

Phages are viruses that infect bacteria. Part of the active phage lifestyle involves a lytic phase, which leads to physical breakdown of host bacteria to allow escape of progeny virus. The application of lytic phages to kill pathogenic bacteria is called phage therapy. Lytic phages of particular pathogens have been cultivated and administered to treat infections in both humans and animals [18]. In United States, phage therapy has been developed and used for the treatment of food borne pathogens in animals [19] and for biocontrol of plant pathogens [20]. Phage therapy is much more specific to the targeted bacteria thus unintended effects on non target bacteria are minimal. One way to tailor the therapeutics of phage therapy is to engineer the activities of specific subunits of a phage [21]. *E.g* endolysins are produced by phages to cleave bonds in the peptidoglycan layer, which permeabilizes the cell wall and causes lysis. One challenge posed by endolysins is tht they are mostly effective against Gram positive bacteria because of the exposed peptidoglycan layer of these bacteria. However, recent progress has been made in characterizing and developing endolysins against Gram negative pathogens [22]. Other types of peptidoglycan hydrolases including exolysins, offer additional therapeutic potential [23].

Bacteriocins

Antimicrobial peptides (AMPs) are increasingly of interest as alternatives to classical antibiotics. A subcategory of AMPs that lacks this drawback is the bacteriocins. Similar to phage encoded endolysins, bacteriocins function by inserting themselves into plasma membrane of target bacteria, forming pores and causing lysis. Many commensal bacteria endogenosly produce bacteriocins, *e.g*., one group of commensal microbes, the lactic acid bacteria (LAB) produce bacteriocin nisin A, which owing to is bactericidal activity is currently used in over 50 countries as a food preservative. Bacteriocins can be used effectively in treatment of human pathogens *e.g*., a bacteriocin produced by *Enterococcus faecium* is effective against Vancomycin-Resistant Enterococcus (VRE) strains [24]. This bacteriocin has been shown to inhibit 29 different strains of VRE including several strains that are classified as pandrug resistant.

Predatory Bacteria

Predatory bacteria are unconventional compared to the bacterial viruses discussed before but they present an interesting possibility for an antibiotic alternative. Many different types of predatory bacteria have been identified but the Bdellovibrio and the Like organisms (BALO) show particular promise. BALOs are motile proteobacteria that obligatory predate Gram negative bacteria for energy and nutrients [25,26]. The latter presents a therapeutic advantage because biofilms are a treatment challenge in both human and animal infections as biofilmic bacteria are upto 1000 times less sensitive to antimicrobials than planktonic cells [27].

BALOs are used in targeting another group of recalcitrant infections (*e.g* polymicrobial cystic fibrosis), the multidrug resistant pathogens including *Acinetobacter baumannii, E.coli, K. pneumoniae, P.aeruginosa, Proteus* spps [28]. Evidences suggest that BALOS and other predatory organisms can colonize the mammalian intestinal tract and serve an amphibiotic purpose [25]. *E.g* in chickens challenged with *Salmonella enterica* and treated with orally administered BALOs, faecal *Salmonella enterica* populations declined with a concurrent reduction in inflammation [29]. BALOs have unique LPS structure that includes an uncharged version of lipid A which is less endotoxogenic than LPS of *E. coli* having low affinity for human LPS receptor resulting in limited immune response.

Reactive Oxygen Technology

This is normally generated by our cells as a byproduct of oxygen metabolism. Based on its reactive oxygen technology, RO101 is applied in the form of gel directly to the site of infection. Reactive oxygen becomes activated upon contact with water and body fluids killing any bacteria present. Liquid powder and aerosol forms are in development. The remarkable aspect of Reactive Oxygen Technology is its strong antimicrobial activity against all major multi drug resistant bacteria commented Matoke Holding'S chief Scientific Adviser, Matthew Dryden [30].

Sequence- Specific Antimicrobials

Antibiotics are weapons of mass destruction: extremely powerful and imprecise. However, with eligobiotics we can precisely intervene on the microbiome-targeting specific bacteria for interventions of our choice. It can be modified to target only those sequences found in the target pathogenic bacteria causing the infection, leaving other strains unharmed. It can even be programmed to kill only those bacteria that are resistant to antibiotics, by targeting DNA [30].

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Egg laying mammal - novel antimicrobial protein

A novel Anti-Microbial Protein (AMP) found in milk of egg laying mammal Echidna can be used as alternative to antibiotics used in livestock. Scientists team at CSIR have shown that this protein creates punctures in the cell membranes of multiple bacterial sps. He has shown that AMP from Echidna is potent against mastitis causing bacteria in livestock.

Use of Vaccines

There are several reasons to consider vaccines among the most promising preventative methods to address the challenges of AMR: First, vaccines can directly prevent infections caused by devastating AMR pathogens. Finally, the use of vaccines prevents the proliferation of bacteria, which do not reach the high numbers necessary for development of resistant mutations [31]. In the past decade, advancements in the field of immunology, genetics, structural biology and microbiology has allowed the development of vaccine technologies to greatly improve the probability to prevent infections caused by obstinate AMR pathogens including *M. tuberculosis, S.typhi, E.coli, C. difficile* and *Pseudomonas aeruginosa.*

Monoclonal Antibodies and other Approaches

Given that antibodies can target bacteria, significant effort has been applied to develop antibody therapy as an alternative. One key challenge is that antibodies have a limited spectrum and target only a small number of strains of a specific species. Of all the approaches, mAbs probably have the best opportunity to treat AMR, although each mAb will probably be limited to a specific species of bacteria. This means that treatment will be reserved for second or third line therapy once the infecting organism has been identified. Another alternative approach involves targeting virulence factors (protein or toxin) produced by the bacteria such that they are no longer pathogenic to the host [32]. Drugs intended for another purpose: *E.g* BPH-652, a phosphosulfonate (anticholesterol by targeting enzyme squalene synthase also inhibits Stap. Aureus virulence by inhibiting dehydrosqualene synthase so may be considered against MRSA [33].

Metal ions as Antimicrobials

Metals like mercury, arsenic, gold, copper and silver have been used in various forms as antimicrobials for thousands of years. Copper has been registered at the U.S Environmental Protection Agency as the earliest solid antimicrobial material. Copper is used for the treatment of different *E.coli, MRSA* and *Pseudomonas* infections. Advantage of silver is it has low toxicity to human cells than bacteria. Zinc is found to be active against *Streptococcus pneumonia*, *Campylobacter jejuni etc*. Silver and Zinc act against *Vibrio Cholerae* and enterotoxic *E.coli*. Metal complexes show synergistic activity against bacteria like Copper and chlorhexidine on dental plaque bacteria, Silver nanoparticles and cephalexin against *E.coli* and *S.aureus* [34].

Oligodynamic Effect

Karl Wilhelm discovered the biocidal nature of heavy metals known as oligodynamic effect. Biocidal action occurs even at low concentration. As per this effect metals bind to thiol or amine moiety of cellular proteins and lead to deactivation and precipitation of proteins. Because of high attraction of metal ions by proteins it leads to increase in cellular concentrations and cell death.

Complementary and Alternative Medicine (CAM) as option

Change of diets are related to rapid changes of the human gut microbiome related to the human health and disease status [35]. Several 'normal' diet ingredients are able to positively influence the immune system [36]. Tea Tree Oil (TTO) is an essential oil derived from the leaves of Australian native plant Melaleuca alternifolia and is effective against MRSA in infected wounds [37]. *Asparagus racemosus* might be an alternative to antibiotics during UTI [38]. Several studies describe a list of promising CAM treatments for several infections, based on clinical experience or in vitro studies [39].

Conclusion

AMR is eroding our ability to control infections with traditional antibiotics, there are scientific challenges to develop new treatments at an equivalent rate and new drug development strategies are needed to combat antimicrobial resistance. These challenges include the need to kill rapidly growing organisms that are adept at keeping out xenobiotics and lack of rapid diagnostics leading to empirical treatment of infections. However, new innovations in vaccines and other alternative approaches have potential to provide new tools to address this public health threat. Due to rise in MDR bacteria metal complexation serves as better alternative as it prevents drug resistance and decreases necessary doses. There is some evidence that CAM prevention and treatment strategies can lead to the prescription and consumption of fewer antibiotics.

Application of review: Study of antibiotic resistance and some alternative options.

Review Category: Veterinary Sciences and Animal Husbandry

Acknowledgement / Funding: Authors are thankful to Division of Clinical Veterinary Medicine, Faculty of Veterinary Sciences and Animal Husbandry, Shuhama, Sher-e-Kashmir University of Agricultural Sciences & Technology of Kashmir, Shalimar, 190019, Jammu and Kashmir, India

****Principal Investigator or Chairperson of research: Dr Zubair Akhoon**
University: Sher-e-Kashmir University of Agricultural Sciences & Technology of Kashmir, Shalimar, 190019, Jammu and Kashmir
Research project name or number: Review study

Author Contributions: All authors equally contributed

Author statement: All authors read, reviewed, agreed and approved the final manuscript. Note-All authors agreed that- Written informed consent was obtained from all participants prior to publish / enrolment

Study area / Sample Collection: Division of Clinical Veterinary Medicine, Faculty of Veterinary Sciences and Animal Husbandry, Shuhama

Cultivar / Variety / Breed name: Nil

Conflict of Interest: None declared

Ethical approval: This article does not contain any studies with human participants or animals performed by any of the authors.
Ethical Committee Approval Number: Nil

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