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Review Article

Antimicrobial Resistance in Bacteria- Its Origin and Evolution: A Review

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Abstract

Antibiotic era was started with the great discovery of penicillin which influenced the existence of humanity. Many novel antibiotics were discovered during the year 1950 to 1960, termed as golden era for antibiotics. Soon after the discovery of several antibiotics, antimicrobial resistance had started emerging. With emerging resistance and non-availability of new antibiotics we are heading towards post antibiotic era. As antimicrobial resistance is becoming a global public health threat, we need an alternative therapy to protect human health. To combat this situation, we need to focus on where antimicrobial resistance originated and the factors associated with its spread. In this review, we have highlighted the history behind origin of antimicrobial resistance, its evolution timeline, drivers of antimicrobial resistance, mechanism of resistance developed and alternative approaches and interventions to combat with this situation keeping an eye on the Indian scenario as well.

Keywords: Antimicrobial Resistance, Alternative Therapy, Evolution

Introduction

Discovery of antibiotics was a heralded victory of mankind against the disease and death. In 1928, the era of antibiotics began with discovery of penicillin by Alexander Fleming and was followed by rapid growth in the discovery of other antibiotics like streptomycin, tetracyclines and fluoroquinolones up to 1970s (Saran *et al.,* 2020). However, the invention of new antibiotics and emergence of antimicrobial resistance occurred side by side (Davies and Davies, 2010; Morehead and Scarbrough, 2018). Now we are heading towards post antibiotic era because very few new antibiotics has been discovered after 1980s. During this period researcher and many pharmaceutical companies changed their approach to combat emerging resistance of pathogens to antibiotics and mainly focused on modification of existing antibiotics. Due to scientific, regulatory, and economic hurdles, many pharmaceutical companies had abandoned antibiotic discovery (Blaser *et al*., 2011; Luepke *et al*., 2017). Antimicrobial resistance occurs when microbes evolve mechanisms that protect them from the effects of antibiotics. There are several factors which affect the emergence of resistance like environmental, social and cultural factor. In near future little injuries may cause death, so it's a high time now to put efforts to combat resistance (WHO, 2018a). Humans and animals as a whole may face multi-drug resistant (MDR) epidemics similar to cholera and tuberculosis epidemics we experienced in the past (WHO, 2018a).

Recently, increased resistance was reported against several serious and common infection causing bacteria worldwide by the Global Antimicrobial Surveillance System (WHO, 2018b). In addition, every year seven lakh people lose their lives due to antimicrobial resistance infection, but the number may increase up to 10 million per year by 2050 (O'Neill, 2016). Antimicrobial resistance also results in 25,000 and 23,000 deaths every year in high-income countries of Europe and USA, respectively (CDC, 2019). Similarly, in middle- and low-income countries like India and Thailand, antimicrobial resistance infection were responsible for the deaths of 58,000 children and 38,000 adults, respectively (CDC, 2019). An estimated expense of whopping 1.5 million USD is caused by antimicrobial resistance (Ali *et al.,* 2018). In the coming decades many people will die because of antimicrobial resistance, so to prevent millions of deaths we need to develop alternative therapies to antibiotics. In this review, we have focused on the background behind origin of antimicrobial resistance and its evolution on macro and micro level since its discovery.

History: Origin of Antimicrobials and Antimicrobial Resistance

Soon after the discovery of antibiotics, emergence of resistance was not far behind. Penicillin was the first antibiotic to be discovered. However, researchers have found traces of tetracycline in skeleton of mummies in ancient Egypt far before the discovery of penicillin (Bushak, 2016). Traces of tetracyclines were evident in thousands of years old skeletons from Sudanese Nubia, because it gets easily settle into bones and tooth enamel (Counsell, 2006). Artemisinin, an antimalarial drug, was used in ancient Chinese medicine. Along with this, herbalists also used mouldy bread to prevent wounds from getting infected (Bushak, 2016). On the basis of this evidence, one can question on the exact time period for origin of antimicrobials. While receiving the Nobel prize, Alexander Fleming mentioned about the resistance phenomenon and he added that microbes will not show any resistance outside body but they can develop resistance inside the body (Tenover, 2006). Staphylococcus resistance to penicillin was identified even before its wide spread use in population (Hwang and Gums, 2016). This invention can prove that bacteria have some intrinsic mechanism to develop resistance and it might be existing over thousands of years. Although the genes responsible for resistance to several classes of antibiotics were reported before the discovery of novel antibiotic penicillin (Bushak, 2016). Resistance leads to the arrival of superbugs due to unnecessary antibiotic prescription and its imprudent use because of natural selection phenomenon in microbes. So, the question "What came first the antimicrobials or antimicrobial resistance" is still persisting.

Evolution of Resistance

Evolution is the change in the characteristics of a species over several generations and relies on the process of natural selection. Bacterial resistance has evolved over a thousand of year. Bacteria likely have an intrinsic lodging for resistance stored within their genome. So, the development of resistance is a natural process and can be accelerate with many external factors. Broadly evolution of antimicrobial resistance can be explained as macrolevel and microlevel of evolution.

Macrolevel Evolution of Antimicrobial Resistance

On a macro level the factors responsible for the evolution are described below-

1. Scale of Human Antimicrobials Use

The increasing trend in consumption of antibiotics in population is one of the major factors responsible for evolution of antimicrobial resistance. Globally, India has been the largest consumer of antibiotics in terms of total tonnage, although, the per capita usage (7.5 units per capita) is very less as compared to other developed nations like Australia and New Zealand (87 and 70 units per capita respectively) (Van Boeckel *et al.*, 2015; Laxminarayan *et al.*, 2016). The consumption pattern of antibiotics varies between economies. Developing and developed countries have different issues to be addressed in terms of antibiotic usage, as different types of antibiotic have been used across globe to treat the infection with diversified aetiologies. Thus, large scale use of broad-spectrum antibiotics in human population helps in evolution of resistant pathogens. As, its use can help in development of resistance in other beneficial flora and pathogenic bacteria. This diversification urges the new antimicrobial resistance action plans to address this problem (Versporten *et al.,* 2014; Gelband *et al.,* 2015). The forecast and projections by several researchers point towards an increase in the consumption in near future (Manyi-Loh *et al.,* 2018).

2. Scale of Antimicrobial Use in Animals

Antibiotics are important tool for maintaining animal health and welfare. These are often dispensed to treat or prevent infections in herds/flocks and also added in food as a growth promotor. Around two third (approximately 65,000 tons out of 100,000 tons) of antibiotics produced worldwide annually had been used in livestock sector (Gelband *et al.*, 2015). This usage in livestock and food animals is again suggested to rise by 2030 (Cuong *et al.*, 2018). Most of the managemental infection in livestock causing severe economic losses are treated with antibiotics. The use of antibiotics helps in inducing resistance in normal microbiota of animals (VKM Report, 2015)**.** So, the prudent use of antibiotic in livestock sector can help to minimize this problem. By acquiring good farm practices, regular monitoring of antibiotic residues in food of animal origin, organic livestock production and using alternatives to antibiotic growth promoter can help to prevent emergence of resistant pathogens (Thakur *et al*., 2019).

3. Environmental Pollution

Wastewater is one of the main sources of resistant bacteria and it also promotes in evolution of many resistant bacteria. Humans excrete antibiotics in their biological active form through urine and faeces (Verlicchi and Zambello, 2014; Zhang *et al.*, 2015). This excreted antibiotic enters in waste water treatment plants (WWTP) which undergoes biodegradation (Chen *et al.,* 2013); absorption to sewage sludge (Li and Zhang, 2010; Ahmed *et al.*, 2015) and exit in the effluent unchanged (Rivera-Utrilla *et al.*, 2013; Luo *et al.,* 2014). Seasonal variation has been reported in level of antibiotics in wastewater in different countries (Al-Riyami *et al.,* 2018). Along with this, greywater from bathing or washing dishes or laundering clothes (Finley *et al.,* 2009; UNESCO-IHE, 2011), reclaimed water (WWTP effluent undergone secondary treatment) and blackwater (recycled, treated sewage effluent) (Kinney *et al.,* 2006; Dodgen and Zheng, 2016) evident the presence of organisms like *Klebsiella pneumoniae, Pseudomonas aeruginosa*, faecal coliforms and faecal streptococci which contribute towards the spread of antimicrobial resistant bacteria and resistant genes (Troiano *et al.,* 2018).

4. Veterinary and Livestock Sector

In livestock sector different managemental activities involve in evolution and spreading of resistant bacteria. Antibiotics are extensively used as a growth promoter to cope up with increasing demand for food of animal origin. However, wide use of subtherapeutic dosage of antibiotic as a growth promoter helps in emerging resistant bacteria (Kumar *et al.*, 2018). Animals excrete a wide range of antibiotics i.e., about 30 to 90% into the manure and urine (Sarmah *et al.,* 2006; Berendsen *et al.,* 2018). These excreta help in contamination of environment with antimicrobial resistant bacteria (Wichmann *et al.,* 2014). Another major source includes bedding and soil around infected animal. It is observed that resistant genes get transmitted through contaminated bedding and soil (Kyselková *et al.,* 2015; Mitchell *et al.,* 2015; Liu *et al.,* 2016). The persistence of antibiotics in soil serve as a continuous source of resistant bacteria (Muhammad *et al.,* 2020). Fluoroquinolones, sulphonamides and tetracycline are commonly found classes of antibiotics in poultry litter (Van Epps and Blaney, 2016). The elements like continuous presence and spread of antibiotics into environment, selection of resistant bacteria in environment and transmission of acquired resistant microbes assist in evolution of antimicrobial resistance (Liu *et al.,* 2016).

5. Agriculture, Apiculture and Horticulture Sectors

In agriculture sector, antibiotics have been used for treating certain bacterial diseases of fruits, vegetables and ornamental plants. Use of antibiotics in agricultural land may increase the amount of antimicrobial resistant gene in the gene pool and in the food chain **(**McManus *et al*., 2002). The over use of antibiotics in agricultural practices like honey production often leads to contamination of product with antibiotics. This contamination can contribute in emergence of antimicrobial resistance in human population (Kumar *et al*., 2020). Another possibility is the presence of antibiotics in the manure used for composting and biogas production which can become a potential source for emergence for antimicrobial resistance (Van Epps and Blaney, 2016). It is observed that agricultural and animal husbandry has vital role in evolution of antimicrobial resistance (Van Epps and Blaney, 2016).

Micro (Molecular) Evolution of Antimicrobial Resistance

Resistance is mainly of two types- intrinsic and acquired. Intrinsic resistance is universally present within the genome of the bacterial species while acquired resistance is developed by acquisition of new genetic material or through mutation in bacterial genome (Hollenbeck and Rice, 2012).

1. Intrinsic Resistance

Intrinsic resistance is developed mainly by antimicrobial selection pressure (Cox and Wright, 2013). Some environmental organisms which naturally carries resistance genes help in appearance of intrinsic resistance whereas this type of resistance emerges because of ancient and long-term use of antibiotics in clinical settings (D’Costa *et al.,* 2011; Cox and Wright, 2013). There is high risk of transmission of resistance from environmental microorganism to the pathogenic organisms. It is observed that there are many active biochemicals exist in environment like bacterial lipocalins and other constituents of parvomes which contribute to intrinsic resistance (Ali *et al.,* 2018). However, the reason behind this antimicrobial resistance is still not clearly identified and further research is going on (Davies and Davies, 2010).

2. Acquired Resistance

Acquired resistance takes major part in evolution of antimicrobial resistance. The mechanism involved in acquired resistance is majorly through mobile genetic elements (MGEs). There are three ways through with resistance can transmit in between cells i.e., transformation, conjugation and transduction (Sommer *et al.,* 2017). MGEs can transmit freely from resistant cells to other sensitive cells or it can get integrated into the cells (Sommer *et al.,* 2017). Intracellular elements which helps in spreading of antimicrobial resistance includes transposons, insertion sequences and integrons (Siguier *et al.,* 2014). Biofilms produced by bacterial population on surfaces play an important role in resistance to antibiotics.

Table 1: List of different mechanism of antimicrobial resistance in various pathogenic bacteria

S. No.	Mechanism of Resistance	Antibiotics and their resistant organisms	References
1	Modification of cell wall	*P. aeruginosa*- Imipenem, *E. aerogenes*a & *Klebsiella* -Imipenem, Gram -ve bacteria-Aminoglycosides, Gram -ve bacteria- Quinolones.	Alekshun and Levy, 2007
2	Efflux Pump	*E. coli* & *Enterobacteriaceae*- Tetracyclines, *Enterobacteriaceae*-Chloramphenicol, Staphylococci-Macrolides, *S. aureus* & *S. pneumoniae* -fluoroquinolones.	Nsofor, 2016
3	Enzyme degradation	*Enterobacteriaceae* Chloramphenicol, Gram -ve & +ve bacteria Aminoglycosides.	Munita and Arias, 2016
4	Target modification	*S. pneumoniae*, *Neisseria gonorrheae*, Group A streptococci, *Listeria monocytogenes*- MRSA, *E. faecium* and *E. faecalis*-Fluoroquinolones.	Munita and Arias, 2016

Biofilms in food processing plants has potential to spread the resistant bacterial population and the antimicrobial resistant genes (ARGs) along the food chain. The interaction between biofilms and efflux pumps needs to be clearly elucidated in order to tackle resistance mechanisms in biofilms (Singh *et al.*, 2017). There are four major bacterial resistance mechanism through which bacteria developed resistance are mentioned in Table 1.

Along with the macro and micro level of evolution, drivers of resistance take important part in evolution of antimicrobial resistance. Biocides and metals are main drivers of resistance. Presence of biocides and antibiotics alongside the environment allow the co-selection of resistant genes (Webber *et al.*, 2015; Wales and Davies, 2015). In environment, coexistence of metal and antimicrobial resistance shares a common structural and functional resistance systems (Baker-Austin *et al.*, 2006). It is common for a microbe to have both ARGs and metal resistance genes, and it is proved that bacteria carrying metal resistance genes have been shown to more frequently carry antimicrobial resistant gene as compared to those bacteria without metal resistance genes, and these genes can often be found on plasmid (Singer *et al.*, 2016).

Factors Responsible for Antimicrobial Resistance in India

There are several factors which are responsible for current antimicrobial resistance situation in India. Some important factors are as follows.

1. **Irrational use of Antibiotics in Humans:** Irrational antibiotic consumption in population is one of the very important factors responsible for emergence of resistance in susceptible bacteria. Reason behind its emergence is use of antibiotics without prescription, using subtherapeutic doses and also not following complete schedule.

2. **Social Factors and Cultural Activities**: Some social factors and cultural activities are associated with potential acquisition and spread of antimicrobial-resistant bacteria. Several social factors like self-medication and lack of awareness among people and cultural activities like religious mass gathering and pilgrimage may act as the forcing factors for the broader transmission of antimicrobial resistance genes and antimicrobial resistance pathogens (Van Boeckel *et al.*, 2015; Gandra *et al*., 2017; Osterhaus *et al*., 2020).

3. **Pollution Caused by Pharmaceutical Industry**: Effluents from the pharmaceutical industries may contain antibiotics and its residues which further contaminate the rivers and lakes (NORDEA, 2015; Gelband *et al.*, 2015). The Indian pharmaceutical industry supplies 20% of generic drugs, with an estimated 15 billion USD in revenue in 2014 (NORDEA, 2015). With respect to antibiotics, it is estimated that 80% of the antibiotics sold by multinational pharmaceutical companies on the global market are manufactured in India and China (Grace, 2004). As large-scale manufacturing of antibiotic can generate more amount of antibiotic effluents and indirectly can cause emergence of antimicrobial resistance.

4. **Environmental Sanitation**: Poor sanitation plays very important role in antibiotic selection pressure which directly helps in the emergence of resistance (Dixit *et al*., 2019). In India, >50% of the population does not have access to sanitation facilities for safe disposal of human waste (World Bank 2017). Untreated sewage contains a significant number of antibiotic residues and resistant organisms contribute in spread of antimicrobial resistance among human population.

5. **Health Care Related Practices**: The prevalence of various health care associated infections (HAIs) among Indian hospitals ranges from 11% to 83%, in contrast to the World Health Organization (WHO) estimate of about 7% to 12% of the HAI burden among hospitalized patients globally (WHO, 2018b). The health care (hospital) associated infections majorly responsible for spreading resistant organisms to healthy population.

Antimicrobial Resistance Scenario

At present, antimicrobial resistance accounts for a global mortality up to 0.7 million, which are estimated to increase to 10 million by 2050, of which Asia alone may contribute up to 4 million cases. This global threat is looming because of continuous adaptation of pathogen to new host and environment which ultimately leads to increased burden on human and animal health. One Health approach is certainly the need of the hour to tackle this threat which demands a collaborative approach at human-animal-ecosystem interface and that has paved the way for a tripartite partnership of the WHO, OIE and FAO to combat against the antimicrobial resistance (O'Neill, 2016; FAO, 2016: WHO, 2018a).

In India, resistance to fluoroquinolones and third generation cephalosporin was more than 70% in *Acinetobacter baumannii*, *Escherichia coli*, and *Klebsiella pneumonia* and more than 50% in *Pseudomonas aeruginosa* (Gandra *et al.,* 2017). Resistance to carbapenems among various Gram-negative bacteria was extremely high (Gandra *et al.,* 2016). Colistin is considered to be the last reported antibiotic in human medicine, but reports of colistin resistance among Gram-negative bacteria has surfaced in India (Kaur *et al.,* 2017; Pragasam *et al.,* 2017; Manohar *et al.,* 2017).

New Delhi metallo-beta-lactamase (NDM-1) & Extended spectrum beta-lactamases (ESBL) producing Gram-negative bacteria were isolated from mastitis milk of cattle (Ghatak *et al.,* 2013; Das and Basak, 2017). ESBL-producing *E. coli* were reported from faecal samples of healthy pigs (Samanta *et al.,* 2015). Isolation of vancomycin-resistant *Staphylococcus aureus* strains in mastitic milk samples of cow (Bhattacharyya *et al.,* 2016) have emphasized the current situation in India. Around 80 % of *E. coli* isolates in India are ESBL producers (CDDEP, 2015). Isolation of ESBL producing *E. coli* strains from faecal samples of chicken (Gandra *et al.,* 2017) and chicken meat samples contaminated with *Salmonella* species resistant to multiple antibiotics have also been reported (Naik *et al.,* 2015). Colistin resistance in human beings have been attributed to antibiotic use in poultry feed (Srivastava, 2017; Brower *et al.,* 2017). An increased prevalence of third-generation cephalosporin- resistant *E. coli* has been reported due to hospital wastewater inflow into sewage treatment plant (Akiba *et al.,* 2015).

How to Tackle Antimicrobial Resistance

With increasing public health threat due to antimicrobial resistance there is need of proper regulations and action plan to tackle this problem. Most important way is to spread awareness among people about the use of antibiotics and formulation of appropriate policies. Sanitation and hygiene can help in reducing antimicrobial resistance burden. The unwanted use of antibiotics in agriculture and livestock's sectors should be avoided. The strong surveillance system is an important way to prevent the infection in population and timely detection of any problem related to antimicrobial resistance. Globally, there are organizations which take part in surveillance like the WHO, OIE, FAO etc. There is urgent need for development of rapid diagnostic test to reduce the unwanted prescriptions of antibiotics in both humans and animals. Vaccination can prevent the infectious diseases which indirectly reduce the therapeutic demand for antibiotics, help in reducing the speed of antimicrobial resistance development. So, by overcoming economical hurdles and promoting discoveries of new drugs can help in tackling of antimicrobial resistance issue.

Alternatives of Antimicrobial Therapy

The failure of existing therapeutic antimicrobial agents along with the lacunae in the antimicrobial discovery pipeline, efforts are directed towards the development of alternatives to tackle the issue of antimicrobial resistance. Promising approaches have been reported for addressing bacterial resistance which includes antibodies targeting specific pathogens, phage therapy, exolysins, endolysins including enzybiotics, vaccines, probiotic and prebiotic strains, antimicrobial peptides (AMPs) and phytocompounds.

1. Bacteriophages and lysins therapy – Bacteriophages are natural/engineered viruses that kills or attack bacteria. The lytic bacteriophages are better alternatives for antibiotics to treat bacterial infections. Among the many alternative medicine strategy, bacteriophages are strong candidates to act against the many foodborne pathogens (Gourkhede *et al*., 2020a). Lysins are enzymes that directly & quickly act on bacteria can be use in biofilm eradication (Lusiak-Szelachowska *et al*., 2020).

2. Antimicrobial peptides- AMPs are small biological molecules, having broad spectrum of activity and mostly found in the tissues and organs that are exposed to airborne pathogens and are believed to be the first line of the innate immune defense against viruses, bacteria and fungi (Gourkhede *et al.,* 2020b). It kills cells by disrupting membrane integrity, inhibiting protein, DNA and RNA synthesis or by interacting with certain intracellular targets (Bhoomika *et al*., 2019). AMPs are recently evaluated as effective therapeutic solutions to treat the MDR pathogens of public health significance.

3. Herbs- It acts Synergistically with drugs, inactivate enzyme (Kumari *et al*., 2019). Now a days, herbal drugs are widely evaluated for treatment of drug resistant pathogens.

4. Others: Some other alternatives like probiotics which prevents colonization of pathogenic bacteria, antibody which directly bind to microorganism and kill them, nanoparticles which act synergistically with other

antimicrobial compound (Karthik *et al.*, 2014) and predatory bacteria – egg. *Bdellovibrio bacteriovorus* are widely tested for its antimicrobial activities.

Researchers are working on vaccine preparation that could help to fight against drug-resistant bacteria. Design of live attenuated bacterial whole cell vaccines based on D- glutamase action is under trial. Recent preclinical studies have identified Th17 cells-based vaccine to give protection against MDR infections (Rappuoli *et al.*, 2017).

Conclusion

The emergence of antimicrobial resistant pathogen is creating a public health hazard globally. To counteract this, it is required to take hold of a preliminary steps in combating antimicrobial resistance. It is very important to study about its evolution and how it gets originated. There is a need of development of alternative therapies to antibiotics. To tackle antimicrobial resistance, we need to strengthening surveillance programmes, microbiological laboratory capacities and multinational collaborations should be encouraged.

Conflict of Interests

There is no conflict of interest.

Publisher Disclaimer

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