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ANTIMICROBIAL RESISTANCE AND PROBIOTICS

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ABSTRACT

Antibiotics were discovered either to kill microbes or to inhibit the growth of bacteria causes disease and diminish human health. Several factors like overuse of antibiotics, incomplete course of antibiotics by patients, over- prescription, poor hygiene control in health care units gave birth to resistant microbes against antibiotics. Today antimicrobial resistance is becoming a major concern globally. These resistant microbes are becoming challenge for scientist working on drugs, pharmaceutical industries and healthcare units. Their multi drug resistance ability making several of resistant microbes more complex in dealing and listing them in deadly pathogen list. These microbes are depleting the natural gut environment by promoting gene of resistance to the gut microbiota leads to several health problems. Such new resistance mechanisms are spreading globally threatening our ability to treat common infectious diseases, resulting in prolonged illness, disability and death. Probiotics are live micro-organisms that are generally regarded as safe, can reduce antibiotic consumption and improve human health largely because of their anti-carcinogenic, anti-allergic and anti –inflammatory properties. Introduction of Probiotics can help to resolve this global problem to some extent.

KEYWORDS: Antibiotic, Gut Microbiota, Antimicrobial Resistance, Probiotics.

INTRODUCTION

History of antibiotics started way back in 19th century with discovery of antibiotic "Penicillin" by Alexander Fleming. Antibiotics believed to be a miracle that can conquered the effects of harmful bacteria selectively causes diseases without harming other cells

(Microbiology Society, 2018). Unfortunately, various factors like overuse of antibiotics, incomplete course of antibiotics by patients, over- prescription, extensive use of antibiotics in agriculture leads to emerging resistant microorganisms which is a serious public health concern. Antimicrobial resistance is the ability of microbes to resist against antibiotics. Microbes resist the effectiveness of antibiotic, drugs, chemical preparation and other agents which are used to kill microbes or reduce their number to prevent infection and cure diseases. These resistance microbes then continuously proliferate and multiplies in number resulting in depletion to human health. With resistant microbes it becomes difficult to treat common infectious diseases. If there is large number of microorganisms that become resistance to multi drugs make it difficult and expensive to treat people results in several visits to doctor, hospitalization, long stays in hospitals, and in severe case death also (AIPUA, 2014). Health-care procedures practise by professionals like organ transplantation, diabetes management, chemotherapy and major surgery become at very high risk. Antimicrobial resistance increases the cost of health care and endangered the sustainable development goals.

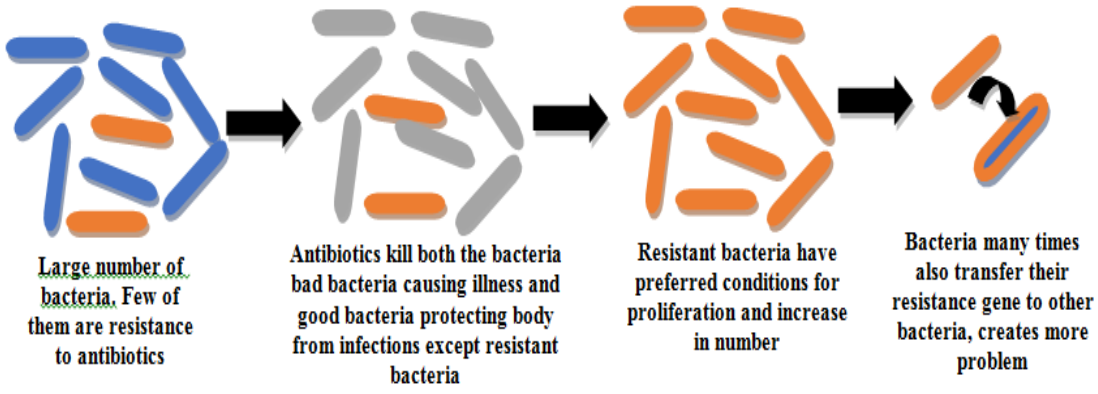

Figure 1: Process of Antibiotic resistance.

MR- A GLOBAL THREAT

Antimicrobial resistance becomes a big threat globally. As antibiotics are becoming unable to treat common infectious disease results in increase illness, disability and in some cases death also. Mentioned are the antibiotics resistant pathogens that need to be curb on priority basis according to WHO (WHO, 2017)-

Carbapenem – Resistant Acinetobacter baumannii

Acinetobacter baumannii is a short, rod shape, Gram-negative, non-motile bacterium belongs to bacterial family Moraxellaceae. It is an opportunistic bacterium that affects people with

weaken immune system and can be easily found in healthcare units like hospitals and long-term care facilities (Evans B.A, 2013). *Acinetobacter* species developed resistance to carbapenem antibiotic through various mechanisms like decreasing permeability, production of class B and D carbapenemase, altering penicillin-binding proteins, and overexpression of efflux pumps (Cherkaoui A, 2015). Complex Characteristics that makes *A. baumannii* a deadliest pathogen includes multidrug resistance phenotype, Lipopolysaccharide barrier, resistance to colistin and serum, presence of Outer membrane protein A (Omp A) for signal processing, Virulence by ethanol, etc. Factors like survival on moist and dry surfaces, its adaptability in health care environment along with intrinsic and acquired antibiotic resistance mechanism makes *A. baumannii* a significant cause of outbreak throughout the world (Perez F, 2011).

Carbapenem – Resistant *Pseudomonas aeruginosa*

Pseudomonas aeruginosa is a rod shape, Gram-negative opportunistic bacterium belongs to bacterial family Pseudomonadaceae. It causes pneumonia, septic shock, urinary tract infection, lung infection, gastrointestinal infection, bloodstream infection, skin and soft tissue infection. (Carbapenem introduced for broad spectrum of antibacterial activity against gram-negative as well as gram-positive bacteria. However, overuse of carbapenem drug and improper dose make it resistant to many of the antibiotics like aminoglycosides, cephalosporins, fluoroquinolones, and carbapenems. *Pseudomonas aeruginosa* can evolve resistance through mechanism like taking advantage of resistance gene on plasmids or through the mutation process. Both strategies limits therapeutic options to develop new drugs for treatment (Lister PD, 2009). Approximately, 440 deaths per year are attributed by the resistant *Pseudomonas aeruginosa* (CDC, 2013).

Carbapenem – resistance Enterobacteriaceae

Enterobacteriaceae is a bacterial family that include well known Gram-negative pathogens like E.coli, Salmonella, Shigella, Enterobacter, Klebsiella, Proteus, etc. Klebsiella spp. and E. coli, two are the most common types of Carbapenem- resistance Enterobacteriaceae. Patients who are taking antibiotics from long term, who are on ventilators, Urinary and Vein catheters are high at risk for Carbapenem- resistance Enterobacteriaceae infections (Teo J, 2012). These bacteria inherit antibiotic resistance gene through mechanisms like carbapenemases (ability to hydrolyze penicillins, cephalosporins, monobactams, and carbapenems), AmpCs and extended-spectrum β-lactamases (ESBLs) (Peleg AY, 2010). Approximately, 600 deaths

per year are attributed through infections caused by carbapenem-resistant Klebsiella spp. and carbapenem-resistant *E. coli* (CDC, 2013).

Vancomycin- resistant Enterococcus faecium

Enterococcus faecium is a Gram-positive opportunistic bacterium belongs to bacterial family Enterococcaceae. The reason behind enterococci bacteria among the forefront in multi-drug resistance is that they evolve in the gastrointestinal tract of invertebrates that naturally feed on organic matter and contains antibiotic and antibiotic producing microbes and another reason is they are better to withstand against stressed conditions like starvation, desiccation etc. as compare to other microbes (Tyne DV, 2017). *Enterococcus faecium* uses secreted factors (carbohydrate, protein and fibrin breaking enzymes), cytosolin, aggregation substances and gelantinase in virulence and has developed resistance against vancomycin and other antibiotics (Higuita A, 2014). About 10,000 (77%) of *Enterococcus faecium* healthcare-associated infections are resistant to Vancomycin that attribute 650 deaths per year (CDC, 2013).

Methicillin – resistant *Staphylococcus aureus*

Staphylococcus aureus is a round shape, gram-positive, facultative anaerobic opportunistic bacterium belongs to bacterial family *Staphylococcaceae*. This bacterium is the part of normal flora of human body found on skin (Wollina U, 2017), in nose (Cole AL, 2018), in intestine (Sollid JUE, 2014). Virulence factors like coagulase, toxins like superantigens, Exfoliative toxins, Fibronectin-Binding Protein A are used by this bacterium to gain resistant against multi-drugs (Netsvyetayeva I, 2014). *Staphylococcus aureus* produces small colony variants during infections makes difficult to detect it in microbiological screening can grow fastly without losing its antibiotic resistance, that causes significant clinical problem (Brandis G, 2017). It is cause of various health problems like skin infections, wound infection, bloodstream infection, pneumonia, bacteremia, sinusitis, sepsis and food poisoning. Methicillin (penicillin derivative) was introduced to decline infections caused by penicillin-resistant strains because of its resistance to β-lactamase but within 2 years from its introduction, first Methicillin Resistant *Staphylococcus aureus* (MRSA) strains were isolated from the hospital of UK and rapidly MRSA became serious concern worldwide (Chatterjee SS, 2013).

Clarithromycin – resistant *Helicobacter pylori*

*Helicobacter pylori i*s a spiral shape, Gram-negative, microaerophilic bacterium belongs to family *Helicobacteraceae.* This bacterium colonizes in human stomach, able to survive highly acidic environment causes several gastric diseases (Burkitt MD, 2017). It is associated with health problems like - chronic gastritis, ulcers and stomach cancer. *Helicobacter pylori* use virulence factors like Cytotoxin-associated gene A product (CagA), Peptidoglycans, cytotoxin gene vacA and outer membrane proteins like blood group antigen binding adhesin (BabA), Sialic acid-binding adhesin (SabA), outer inflammatory protein (OipA) (Hagymás K, 2014). This bacterium resistance to clarithromycin antibiotic is high varying in geographical regions 7.7%-21.5% in Europe (northern & southern countreis), 12% in Latin America 16.4% in the United States, 37.2% in Beijing, China and 55.6% in Japan (Smith SM, 2015).

Fluoroquinolone – resistant *Campylobacter species*

*Campylobacter species i*s a curved (comma or s) shape, Gram-negative bacterium belongs to *Campylobacteraceae* family commonly found in the intestine of animals. It is a leading foodborne pathogen transmitted by contaminated food animal and water consumption (WHO, 2018). Various routes of transmission of diseases to human by *campylobacter*- consumption of contaminated poultry meat, consumption of unpasteurized milk, direct exposure with animals in occupation, contaminated water runoff in agriculture land (Tang Y, 2017). Common symptoms of infection caused by this bacterium are abdominal pain, vomiting, headache, fever, diarrhoea and nausea. Mechanism used by *Campylobacter species* for developing resistance against antibiotics are reduction of accumulation of drug through drug efflux pumps, modification of antibiotics, modification of anti-microbial targets (Shen Z, 2018).

Fluoroquinolone – resistant *Salmonellae*

Salmonellae is a rod-shape, Gram-negative bacterium belongs to family *Enterobacteriaceae*. *Salmonellae* is a genus have approximately 2,500 serotypes which is categorised under two main groups- typhoidal *Salmonellae* and non-typhoidal *salmonellae* (Bulla-Rudas, 2015). Both groups of *salmonellae* are resistant to multi drugs like- Fluoroquinolone, Ceftriaxone, Ciprofloxacin, Ampicillin and azithromycin results in failure of treatment (Harish B, 2011). Fluoroquinolone resistance is mediated by altering drug entry, efflux and altering target enzymes- DNA gyrase and topoisomerase IV (Dahiya S, 2017).

Cephalosporin – resistant *Neisseria gonorrhoeae*

Neisseria gonorrhoeae is a Gram-negative bacterium member of *Neisseriaceae* family. It causes gonorrhoea- sexually transmitted disease, septic arthritis, other gonococcal diseases and can cause infection of eye, throat and genitals. This bacterium is resistance to multi-drugs like cephalosporin, azithromycin and tetracyclin. Resistance to multiple antibiotics resulting in expensive treatment, in case of treatment failure it results in compromised general and reproductive health of the individuals (Unemo M, 2014). *N. gonorrhoeae* uses virulence factors like expression of Por protein, expression Opa protein, elaboration of pili, expression of lipo-oligosaccharide and production of IgA1 protease which makes it easier for bacterium to adapt within the host (Hill SA, 2016).

Penicillin – resistant *Streptococcus pneumoniae*

Streptococcus pneumoniae is a Gram-positive, hamolytic, facultative anaerobic bacterium belongs to family *Streptococcaceae.* This bacterium colonizes in the respiratory tract of human and causes ear and nose infection. It is a leading cause of pneumonia and caused approximately 411,000 deaths worldwide in children less than 5 years (Walker CL, 2013). Resistance is mediated by factors like polysaccharide capsule, pnuemolysin and autolysin enzyme (Keller LE, 2016).

Ampicillin – resistant *Haemophilus influenzae*

Haemophilus influenzae is a Gram-negative, facultative anaerobic pathogenic bacterium belongs to family *Pasteurellaceae.* They are opportunistic bacterium, live normally in the host, usually in nose and throat but causes health problems on getting opportunity. Pathogenic features of *H.influenzae* are inhibition of mucociliary interaction, damage to mucosa by adhering respiratory mucosa, avoidance of mucosal immunity, survival in respiratory tract and ability to attack local tissue (King P, 2012). People with medical conditions like HIV infection, sickle cell disease and patients requiring treatment for cancer-radiation therapy, chemotherapy etc. are at high risk of the infection caused by *H.influenzae* (CDC, 2018).

UNBALANCED GUT MICROBIOTA WITH ANTIBIOTICS

Our gut is home to 100 trillion beneficial and harmful micro-organisms that outnumber body's cell by the factor of 10 (Ohtani N, 2015). Continuous exposure to antibiotics leads to unbalance of this gut microbiota, affecting its composition and functions. Its collateral consequences are loss of important diversity in the gut like diversity of dominant microbes

Firmicutes and *Bacteroidetes* has been reduced; *Actinobacteria*, *Proteobacteria*, *Fusobacteria* and *Verrucomicrobia* which are minor constituents also has been affected and diversity of pathogens like *Enterobacteriaceae*, *Streptococcaceae* has been increased (Lozupone CA, 2013), reduced colonization resistance to pathogens and disease development; increased production of toxins; alteration in gene expression, protein activity and metabolism of gut microbiota and evolution of drug resistant pathogens and spread of antibiotic resistance in the gut. Known and potential harms of antibiotics on Gut Microbiota are as:

What are known harms?

Antibiotic-associated Diarrhoea (AAD)

Clostridium difficile is the major pathogen. Other microorganisms that causes AAD are *Clostridium perfringens*, *Staphylococcus aureus*, *Klebsiella oxytoca*, *Candida species* and *Salmonella species*. Number of these microbes increases in gut in case of AAD (Barbut F, 2002).

***Clostridium difficile* Diarrhoea**

Clostridium difficile is a part of normal flora in 1–3% of healthy adults and 15–20% of infants but starts proliferating in the GI tract with use of broad spectrum antibiotics results in diarrhoea (Goudarzi M, 2014).

Known harms of antibiotics to other body parts-

Tendon rupture

Fluoroquinolone (FQ) antibiotic is commonly prescribed antibiotic for infections like respiratory, urinary and gastrointestinal tract. Tendon rupture is a serious side effect caused by use of Fluoroquinolone antibiotic (Kim GK, 2010).

Cardiac Arrhythmias

Macrolide are broad spectrum antibiotic used against gram-negative bacteria. Long use of macrolide antibiotics like erythromycin, clarithromycin, azithromycin, fidaxomicin and telithromycin increases risk of cardiovascular diseases and can cause cardiac arthythmias (Albert RK, 2014).

a) **What are potential harm?**

- **Impaired immune system**

Our microbiota has intense effect on our immune system. Change in gut microbiota due to administration of antibiotics alters the immune response against infection negatively (Ubeda C, 2012).

- **Childhood Obesity**

Exposure to antibiotics affects the microbiota during pregnancy which in turn alter the microbiota of infant acquired from mother (Cox LM, 2015) and altered microbiota during childhood due to antibiotics treatment leads to change in metabolic function of host and may alter homeostasis mechanism which may results in Obesity (Bailey LC, 2014).

- **Depression**

Our brain and microbiota involves in bidirectional communication which shows the association of microbiota with mood relating problems like stress, anxiety, depression, etc (Winter G, 2018). Antibiotics induce the response of stress hormone (Farzi A, 2018).

- **Increased asthma**

Intestinal microbiota plays an important role in influencing immunity by balancing the activities of helper cell- Th 1 and Th 2 (Ivanov II, 2009). Dysbiosis caused by antibiotics affects immunity by making a difference to tolerance conditions (Riiser A, 2015).

Probiotics- To Restore Antibiotic Induced Microbial Imbalance

Probiotic is a Latin word which means "For Life" (Ozen M, 2015). Probiotics are live microorganisms which on ingesting provide health benefits to the host. The concept of consuming beneficial bacteria for good health and longer lives among Bulgarian farmers was observed by Dr. Elie Metchnikoff, a Russian scientist. He put his findings in a book called "Prolongation of Life" which reveals that consuming fermented products containing lactic acid bacteria could prolong life (Mackowiak PA, 2013). Fermented foods like curd, bread, pickle, Idli, kefir and sauerkraut contains beneficial bacteria which are good for health but cannot be called as Probiotics. In 2001, WHO/FAO gave a universally accepted definition of Probiotics which states that "Live microorganisms which when administered in adequate amount confers health benefits to host" (WHO, 2001). Introduction of Probiotics to intestinal microbiota can be a therapeutic approach to restore the intestinal dysfunction (Hong M, 2018). Roles of Probiotics to maintain our health can be briefed as-

1. Probiotics helps in the digestion of food and better absorption of nutrients required by the body.
2. They help in building the immunity by modulating lymphocytes (B cells & T killer cells) and triggering immune responses.
3. They prevent colonization of pathogens in gut by producing antimicrobial substances like organic acid, bile acids, hydrogen peroxide and bacteriocins to maintain balance between the microorganisms within the intestine.
4. Probiotic produces Short chain fatty acids, enzymes and vitamins like B and K.
5. Probiotics reduce toxins from the body like carcinogens that creates cancer cells.
6. Improves mobility of Intestine.
7. Reduces the risk of infections and allergy by modulating immune cells.

CONCLUSION

Antimicrobial resistance has evolved as a big threat globally. Many factors have influenced this resistance mechanism of microbes like overuse of antibiotics, incomplete course of antibiotics by patients, over- prescription, extensive use of antibiotics in agriculture etc. This review gives an insight to antibiotics resistant pathogens that need to be curb on priority basis according to WHO, known and potential harm to intestinal bacteria caused by antibiotics and role of Probiotics in restoring the gut dysbiosis. Increase in antimicrobial resistance leads to imbalanced intestinal bacteria causes several health problems. In such context, Probiotics can be used as preventive measure as well as a medium to restore the microbial disbalance in the intestine.

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