REVIEW ARTICLE

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Relevance of bacterial normal flora in antimicrobial resistance and incidence of pathogenic infections and how to overcome this resistance

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Abstract

Antibiotic resistance represents a pressing problem, normal flora is destroyed by unnecessary use of antibiotics and as a result, microorganisms with resistance genes multiply. One side effect of misusing antibiotics is the transfer of resistance genes between normal flora and bacterial pathogens, so we need to rationalize our use of antibiotics or find an alternative to them. There are new approaches to combat bacterial resistance such as bacteriophage therapy and its products such as lysins which work as enzymes to degrade bacterial cell wall, in addition, photodynamic therapy is another approach which uses visible light and oxygen present in cells to overcome infections. Also, vaccines can play a role in combating bacterial resistance by protection and reduction of colonization by inducing helper T-cell responses which can be directed against resistant pathogens or against factors of resistance. Plant extracts can be used with antibiotics to inhibit the efflux pump. Cationic antimicrobial peptides are broad-spectrum bactericidal against resistant pathogens.

Key words: Normal flora, antimicrobial resistance.

1. Introduction

There are some factors that contribute to bacterial resistance such as unnecessary use of antibiotics, using a very low dose of antibiotics and consequently, antibiotic doesn't kill microorganisms allowing them to multiply and spread infection,

also resistance can be developed by a too-short duration of antibiotics or incorrect dosage of antibiotic(Pollack and Srinivasan, 2014; Grzybowski, Brona and Kim, 2017). Moreover, antibiotic resistance is natural as resistance genes can encode a protein that could degrade the B-lactams, tetracyclines, and glycopeptide antibiotics (D'Costa et al., 2011).

Genetic mechanisms of resistance

Point mutation in existing genes and acquisition of one or more new genes are responsible for the resistance in methicillin- resistant *Staphylococcus aureus* and vancomycin- resistant *Enterococcus.*

Also, fluoroquinolone resistance in *Streptoococcus pneumonia* is caused by a mutation in the DNA gyrase and topoisomerase IV genes. In addition, mutations in TEM and SHV beta-lactamases on plasmids cause resistance to third-generation cephalosporins in Enterobacteriaceae so, many mutations can turn a susceptible strain to a resistant one. Moreover, altering the balance of microbial flora increases resistance by killing off competing flora (Lipsitch and Samore, 2002). Gene transfer causes acquisition of resistance determinants. Transformation is the uptake of naked DNA which is responsible for the resistance of *Streptococcus pneumonia* to β- lactam via penicillin- binding protein gene. Transduction is caused by bacteriophages. Conjugation involves the transfer of extra- chromosomal or chromosomal DNA by direct cell-to-cell contact.

Conjugative transposons and self-mobile plasmids play an important role in mobilizing other genetic elements that carry resistance determinants. Moreover, bacteria have other mobile elements such as insertion sequence and integrons carrying gene cassettes that lead to antimicrobial resistance (Barbosa and Levy, 2000).

Normal vaginal flora and bacterial vaginosis

Lactobacilli play an important role in maintaining the female genital tract by some mechanisms, such as producing lactic acid that decreases vaginal PH and prevents the occurrence of pathogenic bacteria, hydrogen peroxide, bacteriocin, and surface binding protein which in turn can reduce the risk of bacterial vaginosis. When lactobacilli decrease, there is a reduction of hydrogen peroxide and consequently, overgrowth of facultative anaerobes occurs and bacterial vaginosis happens as facultative anaerobes can displace lactobacilli then rise in vaginal PH(Hawes et al., 1996; Sablon, Contreras and Vandamme, 2000; Witkin, Linhares and Giraldo, 2007; Stojanović, Plećaš and Plešinac, 2012). Furthermore, changes in innate immunity are responsible for the conversion of normal vaginal flora such as lactobacilli to facultative anaerobes that cause bacterial vaginosis (Genc and Onderdonk, 2011; Redelinghuys et al., 2016). Ethnicity is a crucial think about vaginal colonization by various bacteria and women of African ethnicity are more exposed to bacterial vaginosis than Caucasians (Livengood III, 2009; Redelinghuys et al., 2016).

Normal ocular flora and its resistance

Under normal conditions, normal bacterial flora, tears, and eyelids help in protecting the eye surface from foreign microorganisms, consequently, no overgrowth of microorganisms can occur (Grzybowski, Brona and Kim, 2017).

Some factors can make changes in the ocular surface flora such as geographical distribution and climate as in warm, humid weather, positive bacterial rate increases (Rubio, 2004; Shanmuganathan et al., 2005). Another factor that contributes to influence ocular flora is alcoholism and it had been found that with chronic alcoholism, there's a higher incidence of *Staphylococcus aureus* compared to healthy ones(Gunduz et al., 2016). Diabetes also has an effect on ocular flora, an investigation into the ocular flora of diabetic patients, the study found higher rates of methicillin resistance (Suto et al.,

2012). Antibiotic resistance can be developed by mutations and genetic exchange. The presence of genes of intracellular adhesion can form a biofilm in *Staphylococcus aureus* and *Staphylococcus epidermidis* and as a result, causing infection (Fariña et al., 2017).

Oral microbial flora and diseases

The oral microbial flora can maintain the balance in the oral cavity. However, any change in the microbial ecosystem can lead to the growth and proliferation of pathogenic microorganisms like *Streptococcus mutans* and induce oral diseases like dental caries due to alteration in the microflora. In addition, candidiasis is caused by a fungus, *Candida albicans* which is a component of norma oral flora but any change in the oral flora or during immune suppression can result in candidiasis which is an opportunistic fungal infection (Patil et al., 2013).

Role of gastrointestinal microflora in irritable bowel syndrome

Irritable bowel syndrome is characterized by abdominal bloating, variable bowel habits, and abdominal pain. Disruption of intestinal microflora can lead to irritable bowel syndrome due to the mal-fermentation of food because of decreasing numbers of Lactobacilli and bifidobacteria and increasing numbers of facultative organisms such as *Streptococcus* spp, *Escherichia coli* and *Proteus* spp (Madden and Hunter, 2002).

Role of skin microbiota in diseases

Skin microbiota can activate the immune system by secreting antimicrobial peptides. Increasing the Proliferation of commensal bacteria such as *Probionibacterium acnes* and blockage of follicular opening lead to acne vulgaris. Also, the presence of *Helicobacter pylori* causes rosacea which is a chronic inflammatory disease. When the temperature of the skin in rosacea increases because of recurrent flushing, colonization by abnormal skin flora occurs (Murillo and Raoult, 2013). *Staphylococcus epidermidis*, the most common skin microbiota can be converted from microflora to an infectious agent due to extrinsic factors and can cause sepsis, native valve endocarditis and septicemia in the patient risk groups such as those on immunosuppressive therapy (Cogen, Nizet and Gallo, 2008).

Upper respiratory tract flora and acute otitis media

Upper respiratory tract flora can play a role in protecting the upper respiratory tract from colonization by acute otitis media pathogens. Acute otitis media is caused by colonization of mucosal surfaces in the upper respiratory tract by acute otitis media pathogens such as *Streptococcus pneumoniae, Haemophilus influenza,* and *Moraxella catarrhalis* due to lower levels of diversity in the upper respiratory tract flora. These acute otitis media pathogens must compete with commensal flora to cause this disease (Pettigrew et al., 2012).

Probiotics

Probiotic therapy by Lactobacilli can prevent sexually transmitted diseases, preterm labor, and maintain a healthy urogenital tract.

The ingestion of *Lactobacillus rhamnosus* GR-1 and *Lactobacillus fermentum* RC-14 resulted in a normal vaginal flora(Reid et al., 2001). Probiotics have been shown to have a beneficial effect in

preventing gastrointestinal disturbances by adhesion to intestinal cells and resistance to gastric acid. Traveler's diarrhea can be prevented by *Lactobacillus* GG. Normal flora can be suppressed during antibiotic therapy and as a result, resistant strains emerge, this problem can be solved by probiotics that restore the normal flora. Also, probiotics can be used in the treatment of lactose intolerance in lactase deficient patients by *Lactobacillus* strains (Gismondo, Drago and Lombardi, 1999). In addition, probiotics can be used as growth promoters instead of antibiotics. Also, supplements of *Lactobacillus acidophilus* can be used in treatment of constipation (AFRC, 1989). Furthermore, probiotics have anti- cancer activity. Oral administration of *Bacillus polyfermenticus*, a commercially probiotic bacterium stimulates IgG production and exerts antiproliferative effects on colon cancer cells. Moreover, the consumption of probiotics, yogurt, fermented milk, or any other dairy products containing *Lactobacillus* or *Bifidobacterium* may prevent colon cancer (Ma et al., 2010).

Gut microbiota and cancer

The gut microbiota plays a role in the production of vitamins such as pantothenic acid, pyridoxine (vitamin B6), menaquinone (vitamin K2), vitamin B12, niacin, riboflavin and thiamine, digestion of metabolizable substrates, and stimulation of the immune system (McFarland, 2000). The probiotic *Lactobacillus rhamnosus* GG (LGG) is considered a supportive treatment for chemotherapy-associated gastrointestinal toxicity due to its ability to restore gut microbial balance. In addition, LGG is able to counteract cancer growth by anti-proliferative effects. Moreover, it can enhance the immune system to eliminate newly cancer cells (Vivarelli et al., 2019).

New approaches to combat bacterial resistance:

Bacteriophage therapy

Temperate phages can work as gene-delivery vehicles by transferring genetic material to bacteria through integrating their DNA into the bacterial genome, consequently, sensitization of nosocomial pathogens and bacterial flora on the skin of hospital personnel. Furthermore, the resistant pathogens now contain genes carrying sensitivity to antibiotics so resensitization of resistant pathogens occurs. On the other hand, we can use phage products like lysins which work as enzymes to hydrolyze bacterial cell walls, in addition, the T7 phage gene product 0.4 is able to directly prevent FtsZ, an important bacterial protein in the division process(Wang et al., 2003; Margalit et al., 2004; Yosef et al., 2014).

Photodynamic therapy

Photodynamic therapy uses visible light, harmless photosensitizers, and oxygen present in cells to overcome infections, then excitation of photosensitizer molecules occurs and causes the production of reactive oxygen species, consequently, bacterial cell destruction and death happen. On the other hand, multidrug-resistant pathogens can be damaged by using near-infrared light that potentiates the effect of erythromycin, ciprofloxacin, and tetracyclines which are multidrug efflux systems substrates and as a result, efflux inhibition may be due to near- infrared light (Bornstein et al., 2009; Vera et al., 2012).

Furthermore, photodynamic therapy can be used against biofilms, for example, *Helicobacter pylori*, a bacterium that forms biofilms and accumulates porphyrins that act as endogenous photosensitizers. By application of 405 nm endoscopic light, the reduction of CFU counts by 90% happens (Ganz et al., 2005).

Role of vaccines in overcoming the antimicrobial resistance

Vaccines can be used for protection and reduction of colonization by inducing helper T cell responses as in pertussis vaccine that induces th1 and th17 responses (Ross et al., 2013; Lipsitch and Siber, 2016). Furthermore, directing vaccines against resistant pathogens or against factors of resistance is another approach to control antimicrobial resistance (Tekle et al., 2012; Joice and Lipsitch, 2013). Also, we can use vaccines against virulence factors such as toxins and adhesins (Lipsitch and Siber, 2016).

The antimicrobial activity of plant extracts

We can use plant extracts with antibiotics in order to inhibit the efflux pump, resulting in the accumulation of the antibiotic in the bacterial cells (Sibanda and Okoh, 2007). This strategy represents a synergy between antibiotics and plant extracts as plants have some advantages like fewer side effects, inexpensive and can be used as antimicrobial like alkaloids, flavonoids, and tannins (Chanda and Rakholiya, 2011).

Cationic antimicrobial peptides

They are broad-spectrum bactericidal against resistant pathogens, driven from natural sources like bacteria, fungi, insects, fish, and mammals as a response to infection. They can be used to kill Gram-positive bacteria and Gram-negative bacteria, evolved viruses, and even cancer cells in vitro. Furthermore, cationic peptides can induce the uptake of antibiotics and thus show synergy with antibiotics (Hancock and Patrzykat, 2002). Also, peptide antibiotics can be used against malaria, trypanosomiasis, and filariasis (Boman, 1995).

Conclusion:

In order to inhibit bacterial resistance, we need to prevent the transfer of resistance genes between normal flora and bacterial pathogens. Also, we must maintain our normal flora to help us overcoming bacterial resistance by decreasing misusing or overusing antibiotics and choosing the right antibiotic with a specific dose and finishing the course of treatment even if the symptoms are improved. Furthermore, we need to find an alternative to antibiotics and apply new approaches like bacteriophage, natural peptides, photodynamic therapy and vaccines.

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