

A New Light on Antibiotic Resistance

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Last century witnessed one of the biggest changes in health cares, the discovery of antibiotics and consequent revolution in preventing and controlling infection disease treatment. From the 40's to 80's, pharmaceutical companies and health care personnel were convinced that there were already enough antibiotics and infection problem was part of the past and the chapter" in history about infection disease was closed. During this period, the focus in researches for new drugs was shifted to a more life-threatening problems such as cancer, diabetes and heart diseases [1].

The decreasing of antibiotics effectiveness in treating common infections has been observed in recent years, and with the arrival of untreatable strains of resistant bacteria, we may be at the dawn of a post-antibiotic era. United Nation estimates 700,000 people die around the world per year in consequence of drug-resistant bacterial infections such as tuberculosis, and the total global deaths caused by antibiotic-resistant infections are estimated to reach 10 million per year by 2050, with economic losses exceeding US\$100 trillion [2].

The increase of bacteria resistance to antibiotics has appeared as one of the most critical clinical challenges of this century, the urgent need for effective alternatives to antibiotics, especially against the called "ESKAPE" bacteria (*E. faecium*, *S. aureus*, *K. pneumoniae*, *A. baumannii*, *P. aeruginosa* and *Enterobacter* spp.) is urgent. Studies on novelty approaches, such as nanoparticles compounds, cold plasma plume, dye therapy and the use of light, particularly photodynamic therapy, against pathogens are emerging and gaining attention.

Photodynamic therapy (PDT) was discovered more than a century ago and consists in an association of a non-toxic dye (known as a photosensitizer) and low power visible light to produce reactive oxygen species that kills microorganisms or cancer cells. PDT has been used more often in cancer treatment and ophthalmology for age-related macular degeneration. However, now this therapy has been investigated as an approach against microorganisms, especially in dental and dermatological infection. The remaining question is: Why PDT is a promising alternative to treat resistant-bacteria infection?

Antibiotics, as largely suggested by evidences, fail in a long-term analysis due to their single mode/site of action, making possible to bacteria to develop resistance. On the other hand, in PDT when the photosensitizer is illuminated with an appropriated wavelength, their electrons undergo to an excited state and transfer energy to oxygen, resulting in the production of potent oxidizing molecules, such as singlet oxygen, hydroxyl radicals and superoxide anions, which have a broad spectrum of action and can react/damage different microbial targets, like lipids, proteins and nucleic acids. This nonspecific mode of action may turn this therapy very unlikely that bacteria would develop resistance.

Two possible bacterial mechanisms of resistance could be efflux pumps and membrane impermeability, which normally is an efficient way to avoid drugs to access cell interior. In this case, these mechanisms have very little effect against PDT, since reactive oxygen species even when generated at the exterior cell ensure rapid oxidative damage to membrane and are still effective to kill microorganisms [3].

Methylene blue dye is one of the most used photosensitizer for PDT, but other dyes such as Toluidine blue, Rose Bengal, Cristal violet and other compounds like Porphyrins, chlorines, phtalocyanines have also been suggested as antimicrobial photosensitizers. As a light source, low power diode lasers or light emitting diode are almost a unanimous choice.

The use of non-toxic dyes and light has many advantages over chemical antimicrobials:

- Usually they are environmentally friend
- Relatively safe and cheap to produce
- Act in seconds and do not cause damage to surrounding materials
- Act against gram positive and gram-negative bacteria, fungi, virus and parasites
- Act against virulence factors, such as lipopolysaccharides
- There have been no reports of microbial cells developing resistance to PDT

Clinically, PDT approach has been used for superficial infections and the two majors areas of use is dermatology and dentistry. Decontamination of skin wounds and burns, leg ulcer and pressure sore, have clinical trials using PDT protocol. In dentistry, root canal treatment, caries cavity, periodontal pockets and oral mucosa infection also have standardized protocol for treatment.

In conclusion, antimicrobial Photodynamic therapy offers an enormous potential to be a clinical substitute to antibiotic therapy for localized infection, however more effort, support and founding need to be given to “novel approaches” against multi-resistant infections. Moreover, alternative antimicrobial methods, such as PDT, need to continue to grow, attract researchers and clinicians and more clinical trials to obtain additional regulatory approvals around the world in order to became a routine therapy in the post-antibiotic era that is coming.

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