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Photodisinfection Therapy: Essential Technology for Infection Control

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Abstract

Photodisinfection therapy (PDT) is a treatment modality that involves the administration of a light-sensitive compound, known as a photosensitizer (PS), followed by light irradiation at a specific wavelength that excites or "activates" the PS. PDT is minimally invasive and already used clinically to treat a wide range of medical conditions. In its antimicrobial form, (antimicrobial PDT - aPDT) it has been shown to eradicate pathogenic microorganisms such as Gram-positive and Gram-negative bacteria, viruses, protozoa, and fungi and, unlike traditional antibiotics, does not induce resistance following repeated exposures to the therapy (Pedigo et al, 2009; Tavares et al, 2010; Costa et al, 2011; Cabiscol et al, 2000; Lauro et al, 2002; Jori & Coppellotti, 2007; Cassidy et al, 2010; Giuliani et al, 2010; Martins et al, 2018; Al-Mutairi et al, 2018).

For these reasons, we believe aPDT will evolve into an essential tool for infection control and become a vital part of the solution to the global AMR crisis. This report will underscore explain the fundamental principles of aPDT and illustrate the ways in which aPDT can be used to reduce the risk of hospital-acquired infections and improve patient outcomes.

Main Article

Fundamentals of Antimicrobial Photodisinfection Therapy (aPDT)

The first accounts of using light for the treatment of physical illness appeared in Egyptian, Indian, and Chinese writing more than 30 centuries ago (Deniell & Jill, 1991). The first detailed evidence for the antimicrobial activity of certain photosensitizers combined with light was documented in Munich (Raab, 1900), who noticed that the toxic effect of acridine dye on paramecia was greater on sunny days. Overshadowed by the development of antibiotics, another 80 years would pass before seminal work in aPDT began to appear in the literature (Bertoloni et al, 1985; Malik et al, 1990). The discovery and subsequent development of hematoporphyrin in 1841 is considered the most important event in the progress of aPDT (Diels & Arissian, 2011). Second and third-generation porphyrins, porphyrin derivatives, and benzoporphyrins have more recently been developed that improve the efficacy of aPDT (Abdel-Kader, 2016).

The basic electrodynamics (Figure 1) involved in photosensitized reactions involves the absorption of photons by the ground-state PS, causing electrons to be "pumped" to an excited state. This "activated" PS can then engage in many

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different kinds of chemical reactions that are destructive to microbes, such as electron transfer reactions and the formation of radicals, including the potent hydroxyl radical (Type I, redox reactions). A second activation pathway (Type II, peroxidation reactions) also exists, by which energy transfers in a resonant process from a long-lived PS triplet state to surrounding molecular oxygen, itself a ground-state triplet. The oxygen molecules in turn are pumped to their excited state, generating Reactive Oxygen Species (ROS): highly reactive chemical species including singlet oxygen, a powerful oxidizer capable of directly destroying microbes through lethal peroxidative reactions. It has been demonstrated that singlet oxygen can exert potent cytotoxic effects on microbes without being internalized (Dahl et al, 1987). The singlet oxygen lifetime in biological media is short – less than 0.05 µs – due to quenching by water, and therefore the mean diffusion distance of the molecule is less than 0.02 µm before returning to ground state (Moan & Berg, 1991). This short active lifetime localizes the kill to the immediate vicinity of the activated molecule.

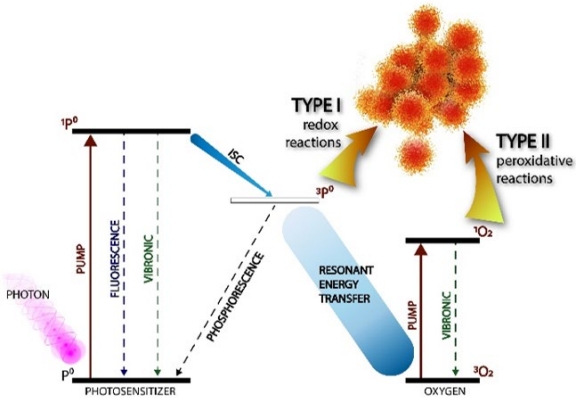


Figure 1: The electrodynamics of photodisinfection therapy. Source: Ondine Biomedical, Inc.

Depending on the chemical nature of the PS, its concentration, local fluid dynamic environment, pre-incubation time, and illumination time, the PS also localizes at different cellular targets. Studies with porphyrin photosensitizers have shown that at short pre-incubation and illumination times, the effects are limited to the microbial cell wall and cytoplasmic membrane, causing damage to transporter systems and transmembrane proteins, leading to cytoplasmic leakage (Malik et al, 1990). At moderate exposure times, a non-porphyrin PS can diffuse into the periplasmic space and damage the cytoplasmic membrane of Gram- negative microbes. Finally, at long exposure times, the PS can intercalate into (and damage) microbial DNA in the cytoplasmic compartment, both at the bacterial chromosome level and in the extrachromosomal plasmids (Valduga et al, 1993).

Photosensitizers are often positively charged to preferentially bind to negatively-charged microbial cell membranes. In contrast, human cells have both positive and negatively charged regions, but overall are electrically neutral. They take up less PS and therefore are more protected from damage (Loebel et al, 2016). The destructive reactions caused by singlet oxygen are therefore selective for the organisms to which the PS adheres. The destructive effect is further amplified by the PDT “bystander” effect (Alexandre et al, 2007) a cooperative inactivation process between cells in a given microcolony, most likely mediated by microbicidal photoproducts or the transfer of lysosomal enzymes from nearby cells.

aPDT for Treatment of Microbial Infection and Disease

The treatment of oral infections by aPDT has been extensively studied for many years and has become a well-established therapeutic option. Several recent reviews have demonstrated its efficacy for the treatment of periodontitis (Joseph et al, 2017; Azaripour et al, 2018; Meimandi et al, 2017), caries

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(Cieplik et al, 2017), endodontic infections (Mohammadi et al, 2017), and peri-implantitis (Ghanem et al, 2016). aPDT has also been found to be effective in the treatment of a variety of other infectious diseases caused by bacteria, fungi and protozoa including brain abscesses (Lombard et al, 1985), acne (Hongcharu et al, 2000; Wiegell et al, 2006; Tuchin et al, 2003; Seo et al, 2016; Tao et al, 2015; Serini et al, 2018), folliculitis (Lee et al, 2010), *H. pylori* (Wilder-Smith et al, 2002), diabetic and skin ulcers (Carrinho et al, 2018; Aspiroz et al, 2017; Lei et al, 2015; Morley et al, 2013; Mannucci et al, 2014), interdigital mycosis (Calzavara-Pinton et al, 2004), keratitis (Amescua et al, 2017), onychomycosis (Morgado et al, 2017), candidiasis (Scwingel et al, 2012), cutaneous leishmaniasis (Asilian & Davami, 2006), oral paracoccidiodomycosis (Dos Santos et al, 2017), and refractory chronic rhinosinusitis (Desrosiers et al, 2013). Treatment of *viral* infections with PDT also has a long clinical history. In the 1970s, a series of clinical studies demonstrated efficacy in treating infections due to the herpes simplex virus (Wainwright, 2003; Kharkwal et al, 2011). The most widely investigated viral infections have been those associated with human papilloma virus (HPV), a group of more than 150 types of virus that affect the skin and mucous membranes. In addition to causing diseases such as respiratory papillomatosis, genital warts, and skin warts (Ohtsuki et al, 2009; Hu et al, 2018), certain HPV types are carcinogenic and can result in cervical, vulvar, penile, and anal intraepithelial neoplasia (Grce & Mravak-Stipetić, 2014; Tommasino, 2014). aPDT with a variety of photosensitizers has been shown to be successful in the treatment of a range of HPV-associated infections including respiratory papillomatosis (Shikowitz et al, 1998; Shikowitz et al, 2005), plantar warts (Schroeter et al, 2005), condylomata acuminate (Wang et al, 2007; Shi et al, 2013), cervical intraepithelial neoplasia (Soergel et al, 2010; Hillemanns et al, 2014), and penile intraepithelial neoplasia (Paoli et al, 2006).

aPDT Is More Than a Microbicide

The damage inflicted by pathogenic microbes on their host, as well as their ability to avoid host defense systems, is mediated by a variety of virulence factors such as exotoxins, endotoxins, capsules, adhesins, invasins, and proteases (Casadevall & Pirofski, 2001). While antibiotics can kill microbes and thereby prevent *further* production of host-damaging molecules, extremely few have any effect on *pre-existing* virulence factors, which means that these molecules may have damaging effects even when the offending microbes have been killed (Lepper et al, 2002).

In contrast to most antibiotics, light-activated PSs are generally able to neutralize microbial virulence factors or reduce their effectiveness or decrease their expression. The ability to modify the biological activities of lipopolysaccharides (LPSs; i.e. endotoxin) is of particular interest because LPSs are potent immunomodulators that can induce secretion of several pro-inflammatory cytokines by host cells (Packer & Wilson, 2000; Pourhajibagher et al, 2018; Pourhajibagher et al, 2017; Shrestha et al, 2015; Giannelli et al, 2017; Tubby et al, 2009; Tseng et al, 2015; Bartolomeu et al, 2016; Calvino-Fernández et al, 2013; Pourhajibagher et al, 2016; Kato et al, 2013; Pereira et al, 2015; Cavaillon, 2018). Activated photosensitizers have been shown to be effective at reducing the activity of LPSs, proteases, and a variety of exotoxins. The ability of aPDT to not only kill the microbes responsible for an infection but also to inactivate or decrease the expression of many of the molecules responsible for host tissue destruction constitutes an important advantage over antibiotics as this combines both antimicrobial and anti- inflammatory approaches into a single treatment.

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aPDT is Safe for Human Use

Numerous pre-clinical and clinical studies have demonstrated that aPDT is safe for use in treating infections in human tissues. For all the energetic reactivity of the ROS, several factors including extremely small time and distance scales, selectivity for anionic microbes, and the inherent resistance to oxidative stress of mammalian cells result in minimal damage to neighboring host tissues (Moan & Berg, 1991; Soukos et al, 1996; Millson et al, 1997; Soergel et al, 2010; Wang et al, 2007). Soukos *et al*. (1996) found that the viability of oral fibroblasts and keratinocytes was unaffected by the low concentration of Toluidine Blue O (TBO) and light dose needed to kill *Streptococcus sanguinis*. A number of photosensitizers, including MB and TBO, have been shown to have no deleterious effects on the gastric mucosa of rats at concentrations and light doses able to kill bacteria (Millson et al, 1997). In a clinical study aimed at detecting tissue damage associated with aPDT, two cycles of aPDT employing aminolevulinic acid esters as the PS were found to exert no damage to the cervix of the test patients (Soergel et al, 2010). The absence of tissue damage following the successful treatment of urethral *condylomata acuminata* (due to HPV) by aPDT using aminolevulinic acid has also been reported (Wang et al, 2007).

aPDT Does Not Induce Microbial Resistance

The generation of ROS in human immune cells (neutrophils, monocytes, and eosinophils) is one of the primary means by which *our own immune system* combats infecting microbes. It should therefore come as no surprise that highly-adaptable microbes have evolved protection strategies against these potent molecules by up-regulating antioxidant enzymes when exposed to ROS (Cabiscol et al, 2000), suggesting one method by which microbes could develop increased resistance to aPDT. However, numerous studies involving repeated exposure of microbes to aPDT and then re-testing the susceptibility of survivors have provided no evidence that resistance development occurs (Pedigo et al, 2009; Tavares et al, 2010; Costa et al, 2011; Cabiscol et al, 2000; Lauro et al, 2002; Jori & Coppellotti, 2007; Cassidy et al, 2010; Giuliani et al, 2010; Martins et al, 2018; Al-Mutairi et al, 2018). In particular, the speed of kill and the external mechanism of ROS appear to limit the ability to develop resistance to aPDT (Maisch, 2015).

In one example utilizing the PS Methylene Blue against MRSA, re-culturing experiments carried out over several consecutive years demonstrated no decrease in susceptibility to aPDT (Figure 2), whereas high-level resistance to oxacillin was established after less than a dozen cycles (Pedigo et al, 2009). This finding has been duplicated in studies with more complex sensitizers (Tavares et al, 2010) and also in viruses, where no increase in resistance was demonstrated after numerous cycles of aPDT (Costa et al, 2011).

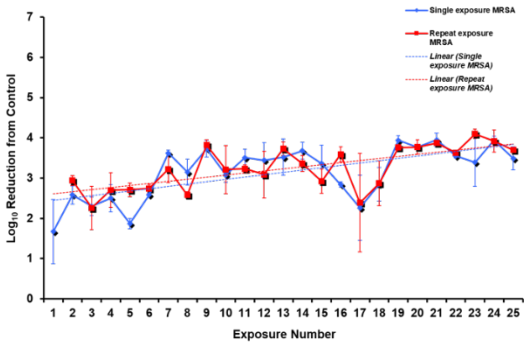


Figure 2: Repeated applications of aPDT to MRSA utilizing Methylene Blue does not promote microbial resistance. Source: Ondine Biomedical, Inc.

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Conclusion

Photodisinfection Therapy is a well-known electrodynamic phenomenon that has become an established therapeutic option for a wide range of medical conditions - from microbial infections to cancer. More than 50 years of clinical use in humans has firmly established the fundamental safety and efficacy of myriad applications of this technology. In particular, *antimicrobial* PDT has tremendous potential to help combat the current global antimicrobial resistance crisis due to its demonstrated clinical efficacy and lack of resistance formation, all while promoting stewardship of existing antibiotics that are increasingly challenging and expensive to develop. aPDT is indeed an essential technology for both the present and the future of infection control.

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