Photodisinfection Therapy: Essential Technology for Infection Control

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Introduction

Antimicrobial resistance (AMR) is considered one of the most serious threats to global health, demanding the development of safe, effective, non-antibiotic therapies for infection control.[1] Because of the incredible cost, time and effort required to develop, approve, and commercialize new antibiotics, the drug development pipeline has stagnated in recent years, even as the generation of antibiotics originally developed in the 1980s and 1990s become increasingly ineffective.[2-5]

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, not harmful, and already used clinically to treat a wide range of medical conditions including acne, psoriasis, age-related macular degeneration, periodontitis, chronic rhinosinusitis, and several cancers such as skin, lung, brain, bladder, bile-duct, esophageal, and head and neck cancers. 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.[128-130,133-139]

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 the AMR threat, describe the urgent need for non-antibiotic approaches to global infection control, 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.

AMR is a Global Health Threat

The UK's 2016 O'Neill report concluded that multi-drug resistance will kill more people by 2050 than cancer, diabetes and cholera combined.[6] The US Centers for Disease Control and Prevention (CDC) estimates that in the US alone, at least 2 million illnesses and 23,000 deaths are caused by AMR.[7] In the European Union, AMR causes 25,000 deaths per year and leads to 2.5 million extra hospital days.[8] The full global impact of AMR is unknown because there is currently no system in place to track it.

AMR is recognized as a critical problem at the highest political levels.[7] In September 2016, a declaration endorsed by Heads of State at the United Nations General Assembly signaled the world's commitment to taking a broad, coordinated approach to address the root causes of antimicrobial resistance. The United Nations Secretary-General has established the *Interagency Coordination Group on Antimicrobial Resistance* to improve coordination between international organizations and to ensure effective global action against this threat to health security.[1] The World Health Organization (WHO) has launched multiple initiatives to help Member States develop national action plans on antimicrobial resistance, including the *Global Antibiotic Research and Development Partnership*, a joint initiative of WHO and the *Drugs for Neglected Diseases Initiative* that encourages research and development through public-private partnerships. By 2023, the partnership aims to develop and deliver up to four new antibiotics, through improvement of *existing* antibiotics and acceleration of the entry of new antibiotic drugs.[1] In 2017, the G20 group of nations launched the *Global R&D Collaboration Hub* on AMR with the goal of identifying important gaps in the development of tools to combat AMR, such as antibiotics, diagnostics, and vaccines.[9] These are just a few examples of the worldwide mobilization of resources to address the expanding threat of AMR.

The Microbes are Winning; Humans Share Much of the Blame

The reality is that microbes (i.e., bacteria, viruses, fungi, protozoa) are currently winning the antibiotic arms race and one major reason comes down to basic biology: microbes, especially bacteria, are capable of reproducing at very high rates. Consider the fact that in approximately 10 hours, a single *Staphylococcus aureus* bacterium (dividing every half hour under optimal conditions *in vitro*) can multiply into a colony numbering more than one million. With a genome of approximately 2.8 million nucleotide base pairs and a mutation rate of 10^{-10} mutations per base, nearly 300 mutations accumulate over those 10 hours. Over 30 hours, the population has expanded so enormously that every single base pair in the entire genome could have mutated[10] - with any one of those mutations theoretically coding for resistance against modern antibiotics. It's easy to see how even the most fundamental natural processes of cell division and genetic mutation contribute to the problem of AMR: the rapid division and mutation capability of bacterial cells allows them to quickly evolve resistance to treatment. Note that this occurs not only for antibiotics which are targeted against bacteria, but also for antiviral and antifungal therapies.[11]

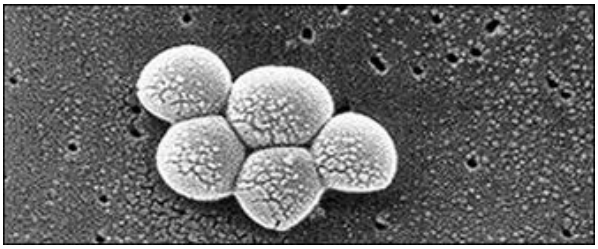

Figure 1: Staphylococcus aureus infections are caused by a bacterium that can divide every half hour in optimal conditions. Theoretically, a single cell can form a colony of more than a million cells in ten hours. Source: Janice Haney Carr/CDC.

An estimated 80-90% of antibiotics are prescribed via oral administration in primary care.[12] Overuse and misuse of antibiotics in primary care is a major cause of increasing AMR, with more than 20% of all antibiotic prescriptions for children and adults in the US written for upper respiratory tract infections or bronchitis, conditions that are almost always viral. Similar rates of unnecessary antibiotic use have been described in Britain. These findings are consistent with results from focus groups among doctors, in which participants have estimated that 10-50% of outpatient antibiotic prescriptions are unnecessary.[13,17] Even in the case of bacterial infections such as those found in otitis media, sinusitis and bronchitis, studies indicate that hundreds of patients require antibiotic treatment to prevent one adverse event[14] and there is little evidence that antibiotic treatment has a significant impact on the duration or severity of symptoms.[15,16] Most primary care clinicians agree that antibiotics are over-prescribed but face complex challenges in changing practice to avoid such prescriptions.[17-19]

Even when antibiotics are appropriately prescribed, many patients fail to adhere to their medication regimens, which leads to incomplete microbial kill and selection for the most resilient microbes in a population.[24-27] In clinical trials, where study participants receive increased compliance support, mean reported adherence rates are nevertheless just 43-78%.[20] Other investigations have found adherence rates of 57-78% by patient report.[21,22] Finally, the prescription regimen itself must be appropriate, with a recent report in the *British Medical Journal* demonstrating that taking antibiotics for longer than necessary also increases the risk of resistance.[23]

The proliferation of antimicrobial agents incorporated into common consumer products (e.g., hand and body soaps, surface cleaners, facial tissues, even mattresses) is also associated with development of AMR. These types of antimicrobial agents differ from traditional broad- spectrum microbicides like soap or chlorine bleach[28] because they often leave surface residues behind, creating conditions that foster the development of resistant bacteria. For example, after spraying and wiping an antibacterial cleaner over a kitchen counter, active microbicidal concentrations are achieved that can linger for significant periods of time, continuing to kill some, but not all, of the bacteria present. Selection pressure for the resistant bacterial populations can then result in those resistant strains becoming predominant in the

environment. As bacteria develop tolerances to surface microbicides, there is also potential for developing tolerance to certain antibiotics. This phenomenon, called "cross-resistance," has already been demonstrated in several laboratory studies using triclosan, one of the most common chemicals found in antibacterial hand cleaners, dishwashing liquids, and other wash products.[29] Triclosan has a specific inhibitory target in bacteria similar to some antibiotics. In 2016, the USFDA issued a final rule under which over-the-counter consumer antiseptic wash products (e.g., liquid, foam, gel hand soaps, bar soaps, body washes) containing many of the most common antibacterial active ingredients, including triclosan and triclocarban, can no longer be marketed because manufacturers haven't proven that those ingredients are both safe for long-term daily use and more effective than plain soap and water in preventing illness and the spread of certain infections.[30]

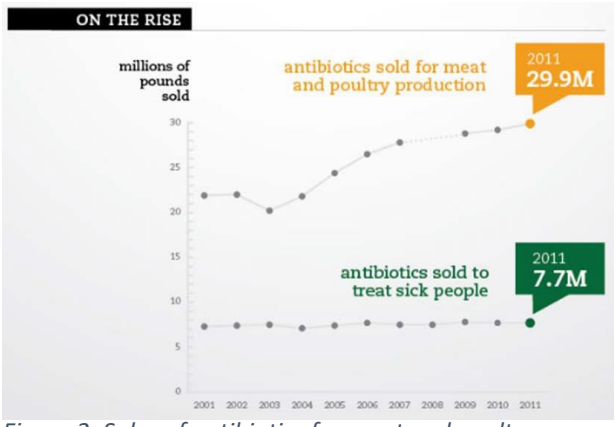

Figure 2: Sales of antibiotics for meat and poultry production in 2011 were 3.9 times greater than antibiotics sold for healthcare use in the United States. Source: The PEW Charitable Trusts, 2013.

Finally, the widespread use of antibiotics in the livestock industry is another major contributor to AMR. In 2011, approximately 80% of the antibiotics sold in the United States were used in meat and poultry production (Figure 2). The vast majority was used on healthy animals to promote growth or prevent disease in crowded or unsanitary conditions.[31] Numerous health and scientific organizations, including the Institute of Medicine, National Research Council, American Medical Association, American Public Health Association, Infectious Disease Society of America, USFDA, and the World Health Organization have concluded that humans are at risk due to resistant bacteria transmitted through direct contact with animals, by exposure to animal manure, through consumption of undercooked meat, and through contact with uncooked meat or surfaces on which meat was being prepared. These so-called "superbugs" can *directly transmit their antibiotic resistance genes* to bacterial species commonly encountered by humans, resulting in antibiotic resistance being 'learned' by microbes that were never exposed to antibiotics themselves.[32-38]

Fewer Antibiotics Are Being Developed

In recent decades, the discovery and development of new antibiotics has slowed dramatically as scientific barriers to drug discovery, regulatory challenges, and diminishing returns on investment have led major drug companies to scale back or abandon their antibiotic research. Consequently, antibiotic discovery, which peaked in the 1950s, has dropped precipitously. In July 2018, just two years after the Swiss pharmaceutical company Novartis announced it would embrace the challenge of searching for cures for life-threatening infections due to AMR,[46] the drug maker announced it would exit antibacterial and antiviral research.[47] This retreat follows a growing trend of big pharmaceutical companies, including AstraZeneca, Sanofi, and Allergan, that are exiting from this type of research, leaving Merck, Roche, GlaxoSmithKline, and Pfizer as the remaining pharmaceutical companies with active antibiotic programs.[48]

Of greater concern is the fact that nearly all antibiotics brought to market over the past 30 years are derived from a limited number of types, or "classes," of antibiotics that were discovered by the mid-1980s (Figure 3). *Every currently available antibiotic is a derivative of a class discovered between the early 1900s and 1984*. This is arguably more concerning than the decline of drug approvals because resistance to one antibiotic often leads to resistance to multiple antibiotics within the same class.[39,40] Only recently have new potential classes of antimicrobials been identified which, in time,

might lead to a much-needed reversal of the trend shown below.[41-44]

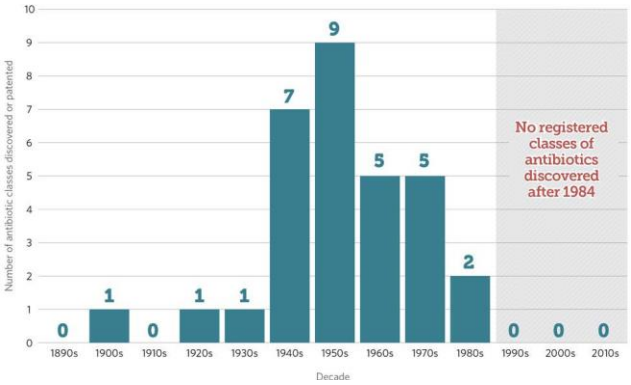

Figure 3: The development of new classes of antibiotics peaked in the 1950s, then sharply declined, resulting in a 30-year drought in the discovery of new classes of antibiotics. Source: The Pew Charitable Trusts,[46] Adapted from Silver et al.[47]

The development of new drugs within *existing classes* of antibiotics has also sharply declined, with new FDA approvals falling from 29 during the 1980s to just nine in the first decade of the 2000s.[45] Just two systemic antibacterial agents were approved for use in humans by the FDA from 2008 through 2011 (Figure 4), compared to sixteen approved from 1983-1987.

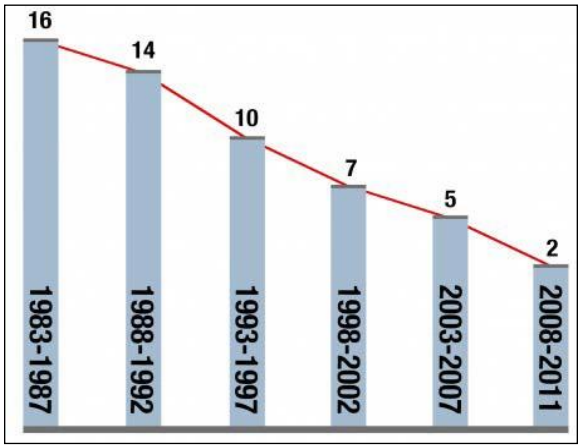

Figure 4: Number of antibiotics approved in the US between 1983 and 2011. Source: European Federation of Pharmaceutical Industries and Associations.

The major cause of the decline in new antibiotic development is the astronomical cost of bringing a new drug to market, coupled with low return on investment. A 2013 Forbes report analyzed the 10-year research spending of 98 pharmaceutical companies and the cost to bring to market 220 new molecular entities. For companies that launched more than three drugs, the median cost per new drug was US$4.2 billion; for those that launched more than four, it was US$5.3 billion.[50] *These numbers were not adjusted for inflation*!

Similarly, a 2013 report published by the Tufts Center for the Study of Drug Development put the cost at US$2.6 billion per drug.[51] What's more, the number of new drugs approved per billion US dollars spent on R&D has halved roughly every 9 years since 1950, falling around 80-fold in inflation-adjusted terms.[49]

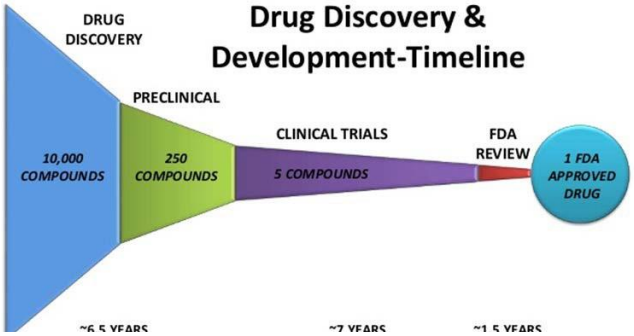

Figure 5: Typical milestones and timelines for FDA approval of new drugs. Source: Ondine Biomedical, Inc.

The second major cause of the decline in new antibiotic development is the generally poor return on investment (ROI) for developing new antibiotics. Pharmaceutical companies can make far greater profits on drugs that can be used regularly without losing effectiveness, such as antidepressants, statins, and anti-inflammatory medications. Hospitals and primary care providers traditionally tend to prescribe proven, inexpensive antibiotics first, delaying the use of newer, more expensive drugs until absolutely necessary. Intentionally limiting the use of novel antibiotics ("black boxing"), limited data on resistance, limited availability and use of diagnostics, and sparse reimbursement all contribute to slow marketing uptake and consequent depression of ROI.

Although the overall antibiotic market is large in volume, it is fragmented into multiple markets by hospital specialty and resistance patterns. Thus, the markets for each of the different antibiotics can be relatively small.[7,52] In a recent analysis for the Department of Health and Human Services, the Eastern Research Group found expected net present values (NPV) for several categories of antibiotic research to be remarkably low and, in some cases, *negative*. In no case did NPV exceed a target benchmark of US$100 million because of the market factors mentioned above.[52] Faced with poor discovery prospects and diminishing ROI, major drug companies have cut back or pulled out of antibiotic research altogether, leaving much of the remaining discovery work to small, "pre-revenue" companies with no products on the market and limited budgets and R&D capacity.[39]

There is an urgent need for increased antibiotic innovation but focusing *only* on innovation will not sustain our ability to address serious infections. Efforts must also be made to prolong the effectiveness of existing antibiotics by implementing sustainable-use measures and limiting antibiotics to therapeutic rather than prophylactic interventions. Other measures include using antibiotics responsibly in individual patients by ensuring they receive the right dose of the right antibiotic at the right time, and by striving to eliminate unnecessary or inappropriate use or exposure, whether in people, agriculture, or the environment.[7] Another key element in the effort to steward and preserve antibiotics is to research, develop, and promote *non-antibiotic* treatments for the treatment and control of infectious diseases.

Fundamentals of Antimicrobial Photodisinfection Therapy (aPDT) [53]

The first detailed evidence for the antimicrobial activity of certain photosensitizers (PSs) combined with light was documented in Munich in 1904[54], although the first accounts appeared in Egyptian, Indian, and Chinese writing 30 centuries before.[55] Overshadowed by the development of antibiotics, another 80 years would pass before seminal work in aPDT began to appear in the literature.[56,57]

The basic electrodynamics (Figure 6) 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 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.[58] 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.[59] This short active lifetime localizes the kill to the immediate vicinity of the activated molecule.

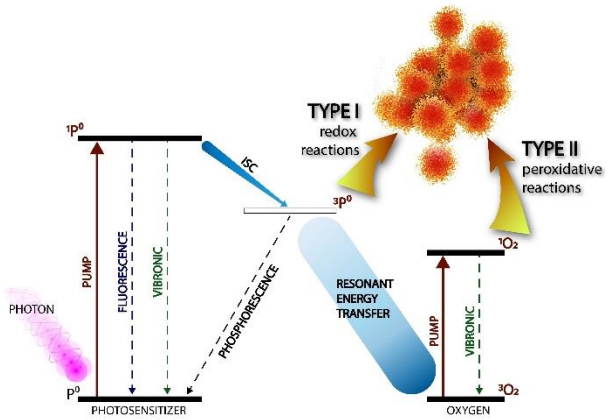

Figure 6: The electrodynamics of photodisinfection therapy. Source: Ondine Biomedical, Inc.

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. 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.[60] At moderate exposure times, the PS can diffuse into the periplasmic space and damage the cytoplasmic membrane of Gram- negative microbes.[131] 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.[131]

Photosensitizers are often positively charged to preferentially bind to negatively-charged microbial cell membranes. In contrast, human cells are zwitterionic, having both positive and negatively charged regions, but overall electrically neutral. They take up less PS and therefore are more protected from damage.[132] 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[61], 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,[62-64] caries,[65] endodontic infections,[66] and peri-implantitis.[67] 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,[68] acne,[69-74] folliculitis,[75] *H. pylori*,[76] diabetic and skin ulcers,[77-81] interdigital mycosis,[82] keratitis [83] onychomycosis,[84] candidiasis,[85] cutaneous leishmaniasis,[86] oral paracoccidiodomycosis,[87] and refractory chronic rhinosinusitis.[88]
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.[89- 92] 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,[93,94] certain HPV types are carcinogenic and can result in cervical, vulvar, penile and anal intraepithelial neoplasia.[95,96] 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,[97,98] plantar warts,[99] condylomata acuminate,[123,100] cervical intraepithelial neoplasia,[122,101] and penile intraepithelial neoplasia.[102]

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.[103] 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 continue to exert damaging

effects even when the offending microbes have been killed. The administration of antibiotics can even have an adverse effect on a patient as large quantities of immunologically-active components of the cell wall (e.g. endotoxins) are liberated during the killing process.[104]

In contrast to most antibiotics, light-activated PSs are generally able to neutralize microbial virulence factors or reduce their effectiveness or decrease their expression.[118] 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.[105-117] 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.

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.[59,120-123] Soukos *et al*. 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*.[120] A number of PSs 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.[121] 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.[122] 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.[123] In the unlikely event that collateral damage to host tissues is a concern, the problem could be circumvented by targeting the PS to the infecting microbe. Several targeting strategies have been developed including the use of antibodies,[124,125] bacteriophages,[126] and microbe-specific peptides.[127]

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,[133] 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.[128-130,133-139] In particular, the speed of kill and the external cidal mechanism of ROS appear to limit the ability to develop resistance to aPDT.

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 7), whereas high-level resistance to oxacillin was established after less than a dozen cycles.[128] This finding has been duplicated in studies with more complex sensitizers[129] and also in viruses, where no increase in resistance was demonstrated after numerous cycles of aPDT.[130]

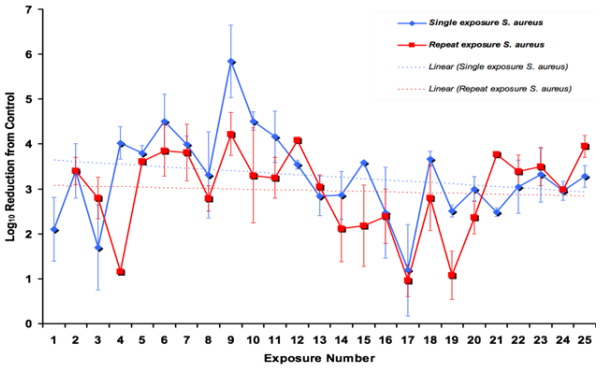

Figure 7: Repeated applications of aPDT to S. aureus utilizing Methylene Blue does not promote microbial resistance. Source: Pedigo et al.[128]

About Ondine Biomedical

Ondine Biomedical Inc. (Ondine) is a Canadian company headquartered in Vancouver, BC, Canada with Research & Development facilities in Bothell, Washington, USA. Founded in 1997, Ondine is dedicated to the development of non-antibiotic, anti-infective photodisinfection therapies for a broad spectrum of bacterial, viral, and fungal infections.

Ondine is the recognized global leader in aPDT technology and has won numerous awards for its work advancing improved patient safety and outcomes. Ondine is the only company with products targeting the top 3 sources of Hospital Acquired Infections (HAIs), including prevention of surgical site infections (SSIs), reduction of ventilator-associated pneumonia (VAP), and reduction of catheter-associated infections (CAIs) where inadequate or no competitive solutions are available. The Company has also developed balloon-catheter based therapies for chronic infections such as Chronic Sinusitis and chronic bladder infections. Most recently the company introduced the SurgENT™ sinus irrigation catheter in the United States and Canada for deep cleansing of sinus debris. Other medical applications and next-generation products in the HAI market are currently under development.

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