Antimicrobial Photodynamic Therapy of Human Skin

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Abstract

Photodynamic therapy (aPDT) has become an important component in the treatment of human infection. This report highlights the scientific literature and clinical guidelines on aPDT in the context of dermatology and considers the treatment of skin infection in all settings now, and in the future. Antibiotic resistance, infection control strategies and technologies able to eradicate microbes without building up new resistance are considered, and their mechanisms of action are described. Published work and National Institute for Clinical Excellence (NICE) Technology appraisals (TA) and research recommendations within Clinical Guidelines were used to identify future applications for PDT. Nanotheranostics can include PDT and were found to be highly relevant, and so treatment combinations and their novel applications will be subject to TA and Randomised Clinical Trials (RCTs). The resistance of some microbes to antibiotics can be reversed through use of supplementary drugs, and so they are likely to remain a mainstay of treatment for skin infection.

The aim of this report is to highlight the utility of Photodynamic therapy (aPDT) in the treatment of human skin infection. Technologies effective in eradicating microbes without building up new resistance are described, alongside their mechanism of action and clinical application. Clinical guidelines on the dermatological manifestations of infection are also considered, particularly the role of standalone PDT, or its co-use with other treatments.

Innate immunity to specific antibiotics exists in microbes because of impenetrable cell membranes, active cell efflux, and/or the presence of certain gene alleles at precise chromosomal locations creating a resistant phenotype. These mechanisms predate the use of antibiotic drugs [idem]. Extrinsic resistance is a property acquired during mutation or experimental recombination, secondary to recombination in-situ when antibiotics are used at subinhibitory concentrations, or via horizontal transfer of r-genes. Multiple and extreme antibiotic resistance has necessitated the use of alternative treatment methods for microbial infection.

PDT is immune to microbial resistance and has been used clinically since the 1970’s to treat a range of infectious diseases. It does not differentiate between microbial strains that are and aren’t resistant to antibiotics. A photosensitiser or pro-drug is applied topically, intravenously, orally, intra-auricularly, or trans vaginally depending on the application. Cell death by necrosis or apoptosis, occurs on absorption of a photon, with substrate, photosensitiser and oxygen level influencing the mode of death. In wound infection and healing, the photosensitiser is applied topically to preserve vasculature to the site by avoiding light absorption by systemically delivered product in the capillaries and arterioles. Transdermal Iontophoresis...
has been used during PDT\(^3\) to reduce incubation time\(^{16}\) or the concentration of anti-inflammatory drugs required compared to localised injections.\(^{11}\)

Electroporation, antimicrobial peptides (AMPs), Photothermal therapy, nitrous oxide (NO) releasing nanoparticles, and cannabidiol\(^{12-16}\) have also proven to be effective treatments for infection and can be used in combination with PDT. Conjugation of known photosensitisers to cationic molecules, AMPs, antibodies, targeted antibiotics, and nanomaterials was initially performed to address accessibility, sensitivity and specificity of PDT.\(^{7,17-20}\) However, some combinations were also found to facilitate imaging by bioluminescence or upon irradiation.\(^{21}\) Diagnostic imaging during clinical treatment is referred to as nanotheranostics.\(^{22}\)

AMPs are directly microbicidal and exert influence on the hosts immune responses.\(^{23}\) DRAMP 2.0 is a detailed database of thousands of known AMPs identifying 76 in clinical use\(^{24}\) and just seven with FDA approval.\(^{25}\) This suggests significant scientific and administrative constraints. Protoporphyrin IX is a naturally occurring photosensitiser stimulated when the prodrug aminovulinic acid (ALA) is applied topically. However, some combinations were also found to facilitate imaging by bioluminescence or upon irradiation.\(^{21}\) Diagnostic imaging during clinical treatment is referred to as nanotheranostics.\(^{22}\)

In vitro studies have demonstrated that antidepressants citalopram and venlafaxine enhance the effect of antibiotics by blocking de novo efflux pumps formed during the resistance process.\(^{21}\) However, fluoxetine has been shown to increase the mutation frequency of \textit{Escherichia coli} to a series of antibiotics\(^{22}\) including chloramphenicol, amoxicillin, tetracycline, fluoroquinolone, aminoglycosides and \(\beta\)-lactams. Consideration of how drugs and supplements inhibit the effect of antibiotics and ultimately exacerbate AMR is now a necessary step in antimicrobial stewardship.

Transmission electron microscopy during deuterporphyrin PDT of \textit{Staphylococcus aureus} (SA) showed profound free radical damage to the cell wall and membrane even at small light and drug doses. A much larger light dose and the addition of the antibiotic oxacillin was required to destroy antibiotic resistant isolates of SA. This effect could not be reproduced for four other antibiotics combined with PDT.\(^{33}\)

Treatment strategies for diabetic foot ulcers are current\(^{34}\) and those appropriate to resource-limited settings are particularly desirable.\(^{35}\) PDT can eradicate multiple bacterial species across large areas, and using daylight leaves only the following operational requirements: a characterised photosensitising ointment; opaque dressings; knowledge of the local solar irradiance and its relationship to fluence (J/cm\(^2\)). Where environments are excessively dark, wet or hot then access to lamps will still be required for PDT provision.

The original 2002 European Guidelines for topical PDT\(^{36}\) highlighted its application in acne and warts. By 2008 cutaneous leishmaniasis (CL) was added to this list,\(^{37}\) with the fungal infection Onychomycosis being introduced in 2012.\(^{38}\) In the 2019 update, all four conditions were recommended for PDT given high quality evidence.\(^{39}\) The British Photodermatology Group concurred with the use of PDT for CL and recalcitrant warts, however, acne is not mentioned and PDT was contraindicated for fungal infections.\(^{40}\) CL in cosmetically sensitive sites was highlighted as being particularly suitable for PDT, in keeping with the European guideline and several daylight treatments were proposed as an alternative to a single lamp session.

The first ever UK NICE clinical guideline on the management of Acne Vulgaris (2021) seeks the trial of light devices to treat its pustules and persistent scarring.\(^{41}\) The same organisation appraised Ambulight to deliver PDT to small non-melanoma skin cancers. It was found to be effective, and less painful than a conventional lamp given its relatively low irradiance.\(^{42}\) While the ambulatory device is more expensive to implement, it would certainly have an antimicrobial application in circumstances where other sources were unavailable, or inappropriate.

Table 4 of my full review of antimicrobial PDT\(^{43}\) presents evidence for complete eradication of warts and acne with PDT, and good results for leg ulcers. Porphyrin as a photosensitiser, or ALA with an extended incubation period were especially effective for warts and acne, even with a small light fluence. Leg ulcers responded to the combination of methylene blue and infrared light with a small light fluence. A much larger light dose and the addition of the antibiotic oxacillin was required to destroy antibiotic resistant isolates of SA. This effect could not be reproduced for four other antibiotics combined with PDT.\(^{33}\)

Cancer research has a relatively well-funded history including optimisation of the technical parameters and combinations for PDT.\(^{44}\) This probably explains the high average efficacy of PDT for skin cancer (82%) compared to more variable outcomes for aPDT\(^{12,45}\) and other clinical applications.\(^{46-50}\) Further methodological research in non-cancer PDT should significantly improve its efficacy and variability.
Table 1: PDT regimen for different diseases

<table>
<thead>
<tr>
<th>Disease</th>
<th>Photosensitizer</th>
<th>Incubation</th>
<th>Illumination</th>
<th>Repeats</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dental Biofilms</td>
<td>Methylene Blue</td>
<td>5 mins</td>
<td>Green or Red</td>
<td>400W</td>
<td>15 mins</td>
</tr>
<tr>
<td>Leg Ulcers</td>
<td>PPA904</td>
<td>15 mins</td>
<td>Infrared</td>
<td>50J/cm²</td>
<td>0 30</td>
</tr>
<tr>
<td>Wounds</td>
<td>Methylene Blue</td>
<td>60 secs</td>
<td>Red</td>
<td>50J/cm²</td>
<td>≤4 29</td>
</tr>
<tr>
<td>Cellulitis</td>
<td>ALA</td>
<td>180 mins</td>
<td>Red</td>
<td>100 mW/cm²</td>
<td>0  c</td>
</tr>
<tr>
<td>Diabetic Foot Ulcers</td>
<td>PPA904</td>
<td>15 mins</td>
<td>Red</td>
<td>50J/cm²</td>
<td>0  30</td>
</tr>
<tr>
<td>Acne</td>
<td>ALA</td>
<td>Short</td>
<td>Blue</td>
<td>13 J/cm²</td>
<td>≤4 40</td>
</tr>
<tr>
<td>Warts</td>
<td>ALA</td>
<td>3 hours</td>
<td>Visible</td>
<td>&gt;100J/cm²</td>
<td>0  c</td>
</tr>
<tr>
<td>Cutaneous Leishmaniasis</td>
<td>ALA</td>
<td>3 hours</td>
<td>Red</td>
<td>50J/cm²</td>
<td>≤4  d</td>
</tr>
<tr>
<td>Onychomycosis</td>
<td>Rose Bengal</td>
<td>NA</td>
<td>White</td>
<td>3.42J/cm²</td>
<td>0  e</td>
</tr>
</tbody>
</table>


Summary

Combinations of treatments for microbial infection will optimise outcomes in future and this could include PDT. More clinical trials will demonstrate the ideal mix of agents and illumination methods for different skin manifestations of microbial infection. Observation of microbes in-situ with changing antibiotic resistance status is desirable and increasingly possible with nanotheranostics. Conventional aPDT with lamps has a large evidence base and an existing infrastructure in many countries and will therefore prevail. Daylight PDT and the use of ambulatory devices could become more popular in regions where resources are limited, subject to the accumulation of high-quality evidence.

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As there was no data collected for this review, data cannot be made available.

There was no code written during this study, and so code cannot be made available.

Ethics Approval was not required as we did not recruit subjects to this review.

Consent to participate was not required as there were no subjects in this review.

Consent to publish was not required as there were no patients in this review.

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