



Antimicrobial Photodynamic Therapy of Human Skin

Alison M Mackay

Division of Musculoskeletal and Dermatological sciences, Faculty of Biology, Medicine and Health, University of Manchester, Manchester, UK.

Article Info

Article Notes

Received: March 14, 2022

Accepted: May 03, 2022

*Correspondence:

*Dr. Alison M Mackay, Division of Musculoskeletal and Dermatological sciences, Faculty of Biology, Medicine and Health, University of Manchester, Manchester, UK; Email: alisonmackay@live.co.uk.

©2022 Mackay AM. This article is distributed under the terms of the Creative Commons Attribution 4.0 International License.

Keywords

Antimicrobial

Photodynamic therapy

Infection

NICE

Guidelines

Nanotheranostics

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.¹ These mechanisms pre-date the use of antibiotic drugs [idem]. Extrinsic resistance is a property acquired during mutation or experimental recombination,² secondary to recombination in-situ when antibiotics are used at subinhibitory concentrations,³ or via horizontal transfer of r-genes.⁴ 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.^{5,6} 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.⁷ In wound infection and healing, the photosensitiser is applied topically to preserve vasculature to the site⁸ by avoiding light absorption by systemically delivered product in the capillaries and arterioles. Transdermal Iontophoresis

has been used during PDT⁹ to reduce incubation time¹⁰ 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 cannabidiol¹²⁻¹⁶ 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 use²⁴ and just seven with FDA approval.²⁵ This suggests significant scientific and administrative constraints. Protoporphyrin IX is a naturally occurring photosensitiser stimulated when the pro-drug aminovulnic acid (ALA) is applied topically. However, the derived hematoporphyrin Benzoporphyrin monoacid ring A (BPD-MA) is thought to be ten times as effective.²⁶ Xanthenes and phenothiazines are effective for a range of microbes, reducing biofilms of *Staphylococcus mutans* at low concentrations and with illumination times of just minutes.²⁷ These photosensitisers are also proven to conquer the rigid cell wall of fungi (idem). Adding inorganic salts potentiates microbial killing²⁸ reducing the light fluence necessary and limiting damage to healthy tissue in clinical practice. Omitting the incubation period lends itself to the treatment of leg ulcers, wounds, and cellulitis.^{29,30}

In vitro studies have demonstrated that antidepressants citalopram and venlafaxine enhance the effect of antibiotics by blocking of de novo efflux pumps formed during the resistance process.³¹ However, fluoxetine has been shown to increase the mutation frequency of *Escherichia coli* to a series of antibiotics³² including chloramphenicol, amoxicillin, tetracycline, fluoroquinolone, aminoglycosides and β -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 deuteroporphyrin PDT of *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

current³⁴ 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 PDT³⁶ 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 PDT⁴³ 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 standard technical parameters, but not when the incubation period was reduced. CL tended to be improved rather than resolved by the treatment regimens investigated. I include a summary table (Table 1) of PDT regimen for different diseases below.

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

Disease	Photosensitizer	Incubation	Illumination			Repeats	Ref
Dental Biofilms	Methylene Blue	5 mins	Green or Red	400W	15 mins	0	a,b
Leg Ulcers	PPA904	15 mins	Infrared	50J/cm ²		0	30
Wounds	Methylene Blue	60 secs	Red	50J/cm ²		≤4	29
Cellulitis	ALA	180 mins	Red	100 mW/cm ²		0	c
Diabetic Foot Ulcers	PPA904	15 mins	Red	50J/cm ²		0	30
Acne	ALA	Short	Blue	13 J/cm ²		≤4	40
Warts	ALA	3 hours	Visible	>100J/cm ²		0	c
Cutaneous Leishmaniasis	ALA	3 hours	Red	50J/cm ²		≤4	d
Onychomycosis	Rose Bengal	NA	White	3.42J/cm ²		0	e

a. Fontana CR, Abernethy AD, Som S, et al. The antibacterial effect of photodynamic therapy in dental plaque-derived biofilms. *J Periodontal Res.* 2009;44(6):751-759. doi:10.1111/j.1600-0765.2008.01187.x

b. Wood S, Metcalf D, Devine D, Robinson C. Erythrosine is a potential photosensitizer for the photodynamic therapy of oral plaque biofilms. *J Antimicrob Chemother.* 2006;57(4):680-684. doi:10.1093/jac/dkl021

c. Ibbotson SH. Topical 5-aminolevulinic acid photodynamic therapy for the treatment of skin conditions other than non-melanoma skin cancer. *The British Journal of Dermatology.* 2002;146(2):178-188.

d. Wang YS, Tay YK, Kwok C, Tan E. Photodynamic therapy with 20% aminolevulinic acid for the treatment of recalcitrant viral warts in an Asian population. *Int J Dermatol.* 2007;46(11):1180-1184.

e. Valkov A, Zinigrad M, Nisnevitch M. Photodynamic Eradication of *Trichophyton rubrum* and *Candida albicans*. *Pathogens.* 2021;10(3):263.

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.

Acknowledgements and Declarations

The author would like to thank her parents Alistair and Margaret Mackay for feeding her thus allowing this manuscript to be prepared.

The author did not receive financial support from any organization for the submitted work.

The author has no conflicts of interest to disclose.

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.

References

- Cox G, Wright GD. Intrinsic antibiotic resistance: mechanisms, origins, challenges and solutions. *Int J Med Microbiol.* 2013 Aug; 303(6-7): 287-92.
- Guerin E, Cambray G, Sanchez-Alberola N, et al. The SOS response controls integron recombination. *Science.* 2009 May 18 22; 324(5930): 1034.
- Guerin E, Cambray G, Da Re S, et al. Les antibiotiques induisent la capture de gènes de résistance par les bactéries [The SOS response controls antibiotic resistance by regulating the integrase of integrons]. *Med Sci (Paris).* 2010 Jan; 26(1): 28-30. French.
- Lerminiaux NA, Cameron ADS. Horizontal transfer of antibiotic resistance genes in clinical environments. *Can J Microbiol.* 2019 Jan; 65(1): 34-44.
- Hamblin MR, Hasan T. (2004). Photodynamic therapy: a new antimicrobial approach to infectious disease? *Photochemical & photobiological sciences: Official journal of the European Photochemistry Association and the European Society for Photobiology.* 3(5), 436-450.
- Hamblin MR. (2016). Antimicrobial photodynamic inactivation: a bright new technique to kill resistant microbes. *Current opinion in microbiology.* 33, 67-73.
- Chen CH, Lu TK. Development and Challenges of Antimicrobial Peptides for Therapeutic Applications. *Antibiotics.* 2020; 9(1): 24.
- Nesi-Reis V, Lera-Nonose D, Oyama J, et al (2018). Contribution of photodynamic therapy in wound healing: 21, 294-305.
- Rhodes LE, Tsoukas MM, Anderson RR, et al. Iontophoretic delivery of ALA provides a quantitative model for ALA pharmacokinetics and PpIX phototoxicity in human skin. *J Invest Dermatol.* 1997 Jan; 108(1): 87-91.
- Mizutani, et al. Photodynamic therapy using direct-current pulsed iontophoresis for 5-aminolevulinic acid application. *23 Photodermatology, Photoimmunology and biomedicine (2009).*

11. Lepak LV. Chapter 7 - Localized Inflammation, Editor(s): Cameron, M and Monroe, LG. *Physical Rehabilitation*, W.B. Saunders, 2007; 117-139.
12. Novickij V, Zinkevičienė, A, Perminaitė E. et al. Non-invasive nanosecond electroporation for biocontrol of surface infections: an in vivo study. *Sci Rep* 8, 14516 (2018).
13. Lei J, Sun L, Huang S, et al. The antimicrobial peptides and their potential clinical applications. *Am J Transl Res.* 2019 Jul 15; 11(7): 3919-3931.
14. Huang X, El-Sayed IH, Qian W, et al. (2006). Cancer cell imaging and photothermal therapy in the near-infrared region by using gold nanorods. *Journal of the American Chemical Society*, 128(6), 2115–2120.
15. A., Yin, R., Tegos, G. P., & Hamblin, M. R. (2013). Antimicrobial strategies centered around reactive oxygen species--bactericidal antibiotics, photodynamic therapy, and beyond. *FEMS microbiology reviews*, 37(6), 955–989.
16. Blaskovich MAT, Kavanagh AM, Elliott AG, et al. The antimicrobial potential of cannabidiol. *Commun Biol* 4, 7 (2021).
17. Klausen M, Ucuncu M, Bradley M. Design of Photosensitizing Agents for Targeted Antimicrobial Photodynamic Therapy. *Molecules.* 2020; 25(22): 5239.
18. Xie S, Manuguri S, Proietti G, et al. (2017). Design and synthesis of theranostic antibiotic nanodrugs that display enhanced antibacterial activity and luminescence. *Proceedings of the National Academy of Sciences of the United States of America*, 114(32), 8464–8469.
19. Lehar S, Pillow T, Xu M, et al. Novel antibody–antibiotic conjugate eliminates intracellular *S. aureus*. *Nature* 527, 323–328 (2015).
20. Hung Le, Christophe Arnoult, Emmanuelle Dé, et al. Antibody-Conjugated Nanocarriers for Targeted Antibiotic Delivery: Application in the Treatment of Bacterial Biofilms *Biomacromolecules* (2021).
21. Seok ki Choi. Photo activation Strategies for Therapeutic 22 Release in Nanodelivery Systems. *Advanced Therapeutics* (2020).
22. Introduction to Nanotheranostics. Subramanian Tamil Selvan, Karthikeyan Narayanan. Springer 2016.
23. Mookherjee N, Anderson MA, Haagsman HP, et al. Antimicrobial host defence peptides: functions and clinical potential. *Nat Rev Drug Discov* 19, 311–332 (2020).
24. Kang X, Dong F, Shi C, et al. (2019). DRAMP 2.0, an updated data repository of antimicrobial peptides. *Scientific data*, 6(1), 148.
25. Chen CH, Lu TK. Development and Challenges of Antimicrobial Peptides for Therapeutic Applications. *Antibiotics.* 2020; 9(1): 24.
26. Richter AM, Jain AK, Canaan AJ, et al. Photosensitizing efficiency of two regioisomers of the benzoporphyrin derivative monoacid ring a (BPD-MA), *Biochemical Pharmacology.* 1992. 43 (11) 2349-2358.
27. Galdino D. et al. Photodynamic optimization by combination of xanthene dyes on different forms of *Streptococcus mutans*: An in vitro study. *Photodiagnosis and Photodynamic Therapy.* 2021. 33: 10291.
28. Kasimova KR, et al. Potentiation of photoinactivation of Gram-positive and Gram-negative bacteria mediated by six phenothiazinium dyes by addition of azide ion. *Photochem Photobiol Sci.* 2014; 13(11): 1541–1548.
29. Bennewitz A, Prinz M, Wollina Uwe. Photodynamic therapy to improve wound healing in acute and chronic wounds: Tricyclic dye combined with low level 810 nm diode laser irradiation. *Kosmetische Medizin.* 2013; 34: 208-215.
30. Morley S, et al. Phase IIa randomized, placebo-controlled study of antimicrobial photodynamic therapy in bacterially colonized, chronic leg ulcers and diabetic foot ulcers: a new approach to antimicrobial therapy. *Br J Dermatol.* 2013; 168(3): 617-24.
31. Ayaz M. et al. Citalopram and venlafaxine differentially augments antimicrobial properties of antibiotics. *Acta poloniae pharmaceutica.* 2015; 72: 1269-1278.
32. Jin M, Lu J, Chen Z, et al. (2018). Antidepressant fluoxetine induces multiple antibiotics resistance in *Escherichia coli* via ROS-mediated mutagenesis. *Environment international*, 120, 421–430.
33. Iluz N, Maor Y, Keller N, et al. The synergistic effect of PDT and oxacillin on clinical isolates of *Staphylococcus aureus*. *Lasers Surg Med.* 2018; 50(5): 535-551.
34. Armstrong DG, Boulton AJ, Bus S. Diabetic Foot Ulcers and their recurrence. *N Engl J Med* 2017; 376: 67-75.
35. Karabanow AB, et al. (2021). An Analysis of Guideline Consensus for the Prevention, Diagnosis and Management of Diabetic Foot Ulcers. *J Am Podiatr Med Assoc.* 2021 19-175.
36. Morton, CA et al. Guidelines for topical photodynamic therapy: report of a workshop of the British Photodermatology Group. *Br. J of Dermatol.* 2002; 146(4), 552–567.
37. Morton CA, et al. Guidelines for topical photodynamic therapy: update. *Br. J of Dermatol.* 2008; 159(6): 1245–1266.
38. Morton CA, Rolf-Markus S, Alexis S, et al. European guidelines for topical photodynamic therapy part 2: Emerging indications - Field cancerization, photorejuvenation and inflammatory/infective dermatoses. *Journal of the European Academy of Dermatology and Venereology. JEADV.* 2012; 27(6): 672-679.
39. Morton C, et al. 2019. 30 European Dermatology Forum guidelines on topical photodynamic therapy 2019 Part 2: emerging indications - field cancerization, photorejuvenation and inflammatory/infective dermatoses. *Journal of the European Academy of Dermatology and Venereology. JEADV.* 2019; 34 (1): 17-29.
40. Wong T. et al. British Association of Dermatologists and British Photodermatology Group guidelines for topical photodynamic therapy. *Br J Dermatol.* 2018; 180: 730-739.
41. *Acne vulgaris: management.* (2021). National Institute for Health and Care Excellence (NICE).
42. Ambulight PDT for the treatment of non-melanoma skin cancer. (2011). NICE Medical technologies guidance.
43. Mackay AM. The Evolution of Clinical Guidelines for Antimicrobial Photodynamic Therapy of Skin. *Photochem Photobiol Sci.* 2022; 1-11.
44. Cohen DK, Lee PK. Photodynamic Therapy for Non-Melanoma Skin Cancers. *Cancers.* 2016; 8(10): 90.
45. Tang G. et al. Application of Photodynamic Therapy to the Treatment of Atherosclerotic Plaques, *Neurosurgery.* 1003; 32, (3): 438–443.
46. Treatment of Age-Related Macular Degeneration with Photodynamic Therapy (TAP) Study Group Photodynamic therapy of subfoveal choroidal neovascularization in age-related macular degeneration with verteporfin. One-year results of 2 randomized clinical trials-TAP report 1. *Arch Ophthalmol.* 1999; 117: 1329-1345.
47. Barrett's Esophagus: Treatment with 5-Aminolevulinic Acid Photodynamic Therapy, *Gastrointestinal Endoscopy Clinics of North America.* 2000; 10 (3); 421-437
48. Topical photodynamic therapy for psoriasis, Editor(s): Calzavara-Pinton, P, Szeimies, RM, Ortel, B *Comprehensive Series in Photosciences.* 2001; 2: 2259-270,
49. Jenkins MP. et al. Clinical study of adjuvant photodynamic therapy to reduce restenosis following femoral angioplasty. *Br J Surg.* 1999; 86: 1258-1263.
50. Hamblin MR, Hasan T. Photodynamic therapy: a new antimicrobial approach to infectious disease? *Photochem Photobiol Sci.* 2004; 3(5), 436–450.