The evolution of clinical guidelines for antimicrobial photodynamic therapy of skin

Alison M. Mackay¹,²,³

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Abstract
Antimicrobial photodynamic therapy has become an important component in the treatment of human infection. This review considers historical guidelines, and the scientific literature to envisage what future clinical guidelines for treating skin infection might include. Antibiotic resistance, vertical and horizontal infection control strategies and a range of technologies effective in eradicating microbes without building up new resistance are described. The mechanism of action of these treatments and examples of their clinical use are also included. The research recommendations of NICE Guidelines on the dermatological manifestations of microbial infection were also reviewed to identify potential applications for PDT. The resistance of some microbes to antibiotics can be halted, or even reversed through the use of supplementary drugs, and so they are likely to persist as a treatment of infection. Conventional PDT will undoubtedly continue to be used for a range of skin conditions given existing healthcare infrastructure and a large evidence base. Daylight PDT may find broader antimicrobial applications than just Acne and Cutaneous Leishmaniasis, and Ambulatory PDT devices could become popular in regions where resources are limited or daylight exposure is not possible or inappropriate. Nanotheranostics were found to be highly relevant, and often include PDT, however, new treatments and novel applications and combinations of existing treatments will be subject to Clinical Trials.

Graphical abstract

Keywords Antimicrobial · Clinical guideline · Photodynamic therapy · Nanotheranostics · Infection

✉ Alison M. Mackay
alisonmackay@live.co.uk

Extended author information available on the last page of the article
1 Introduction

The aim of this review is to describe why antimicrobial Photodynamic therapy (aPDT) has become an important component in the treatment of human infection and to discuss what future guidelines for its clinical application might include. The emergence of antibiotic resistance has been considered, as have vertical and horizontal infection control strategies [1], and a range of technologies effective in eradicating microbes without building up new resistance. The mechanism of action of these technologies is described and examples of their clinical use summarised. Finally, national and international clinical guidelines on the manifestations of microbial infection and the use of PDT have been studied, including their research recommendations. While consensus on the use of antimicrobial PDT in humans is the ultimate focus of this review, it is first acknowledged that: the methods were developed in the laboratory; [2] many of the basic science investigations were done on murine cohorts; [3] current veterinary indications for PDT are broad ranging and include bacterial infection in domestic animals [4].

Antibiotics were clinically introduced during the Second World War and the emergence of resistant strains of bacteria was described as early as 1959 [5] followed by a detailed study of the underpinning mechanisms revealing several modes of resistance. Innate immunity to specific antibiotics exists in microbes because of impenetrable cell membranes, active cell efflux, and/or the presence of certain gene alleles in specific positions on the chromosome creating a resistant phenotype [6]. These mechanisms predate the use of antibiotic drugs [6]. Extrinsic resistance is an acquired property evolving via mutation, or during experimental recombination [7], when antibiotics are used at subinhibitory concentrations causing recombination [8], or via horizontal transfer of r-genes [9].

Methods of tracing the evolution of microbial strains have been described including phylogenetic trees [10]—retrospective by nature—and prospective in-vivo measurements of the natural course of the nosocomial bacterial infection becoming resistant to a series of antibiotics [11]. Nanotheranostics offers additional insights by allowing observation of microbes in-situ, [12] and during treatment. During the Covid-19 pandemic, infection prevention and control in public places and healthcare has been enhanced [13–16] to minimise the proliferation of the virus. However, antimicrobial stewardship has diminished [17, 18] with the net effect likely to be a worldwide increase in microbial resistance. In their 2010 paper, Davies and Davies [19] highlight the presence of multidrug-resistant bacteria in the biosphere with consequences aggravated by civil unrest, violence, famine, natural disaster and poor hospital practices; and so the net long-term effects of Covid-19 on bacteria, and indeed other microbes, has yet to be realised. Multiple and extreme (a lack of susceptibility to four or more drugs) antibiotic resistance has necessitated the use of alternative treatment methods for microbial infection including electroporation [20]; antimicrobial peptides (AMPs) [21]; photodynamic therapy (PDT) [22]; photothermal therapy [23]; nitrous oxide (NO) releasing nanoparticles [24]; cannabidiol [25]; or combinations of therapies. Electroprogress is a technique where 30–100 V pulses are used for a fraction of a second to create local aqueous permeable regions in between lipid membranes by destabilisation [26], however, its clinical importance have yet to be tested. Accessibility and limitations on sensitivity and specificity of PDT has been addressed by conjugation of known photosensitisers to cationic molecules, AMPs, antibodies, targeted antibiotics or nanomaterials [27–32]. Gold nanorods conjugated with antibodies or AMPs then introduced into the bloodstream and irradiated externally achieve both Photodynamic and Photothermal effects [33, 34]. Polyvalent ligand strategies optimise the yield of any exogenous agent [35] and have been used to achieve simultaneous light-controlled drug release, Photodynamic and Photothermal treatments. The field of nanotheranostics takes the use of nanomaterials a step further by utilising agents with luminescent properties, allowing diagnostic imaging and treatment to be achieved concurrently [36]. Transdermal Iontophoresis is a system for the controlled delivery of pharmaceuticals using small electric currents, and works particularly well for small lipophilic molecules [37]. It has previously been used to facilitate PDT [38] and allow therapy at lower anti-inflammatory drug concentrations than localised injections [39]. For the photosensitising agents of PDT, iontophoresis facilitates a much shorter incubation time before illumination [40]. Even without light, the electrical activation of silver ions (oligodynamic iontophoresis) has shown broad-spectrum antimicrobial activities against bacteria, fungi and viruses [41]. The technique uses a much smaller current than electroporation, therefore reducing the electrical hazards involved [42].

Photodynamic Therapy is immune to resistance, and has been used clinically since the 1970’s to treat a range of cancers and precancerous skin lesions [43]. Age-related Macular Degeneration (AMD) [44, 45], Arthrosclerosis [46], Arthritis [47], Barrett’s Oesophagus [48], Psoriasis [49], and Restenosis [50]. The treatment of Infectious disease using PDT is a relatively recent application that does not discriminate between strains that are and are not resistant to antibiotics [51, 52]. PDT requires a photosensitiser or pro-drug to be applied topically, intravenously or by an expanding range of other routes including oral, intra-auricular injection and transvaginal fibre [53].
is vital that the photosensitiser is applied topically to maximally preserve vasculature to the site [54]; residual product in the proximal capillaries and arterioles following systemic delivery could lead to their destruction during illumination of a site with deeply penetrating light. On absorption of a photon, one of the photosensitisers (PS) two singlet state electrons is temporarily elevated to an excited singlet state creating fluorescence or heat on its return. Alternatively, the electron may have its spin inverted (parallel to its counterpart) creating a new excited triplet state in a process called intersystem crossing. From here, one of two things can happen: (1) The particle reacts directly with the surrounding tissue (substrate) forming a radical anion or cation which then reacts with oxygen in the air to produce reactive oxygen species (ROS); (2) All of the electron’s energy is transferred to oxygen from the air forming singlet oxygen. Both these outcomes result in cell death by necrosis or apoptosis, and the specific substrate, photosensitiser and level of oxygen will influence the ratio of type 1 and 2 reactions [55].

Photosensitisers can be grouped by their chemical composition and Table 1 highlights relevant features of different groups. Protoporphyrin IX is a naturally occurring photosensitiser, whose localised production can be stimulated from the pro-drug aminovulinic acid (ALA). However, the derived hematoporphyrin Benzoporphyrin monoacid ring A (BPD-MA) is thought to be ten times as effective [56]. Xanthenes stand out from the table as being versatile, and when used in combination have been shown to greatly reduce biofilms of Staphylococcus mutans at low concentrations and with short illumination times [57]. Phenothiazines appear equally versatile and their hydrophilicity allows them to conquer the rigid cell wall of fungi [58]; incidentally, where candida infection is localised to the stratum corneum, then illumination with blue light is preferable. The addition of inorganic salts potentiates microbial killing [59] in either type 1 or 2 reactions; azide and potassium iodide have been used with phenothiazines and cationic fullerenes and bromide alongside titanium dioxide nanoparticles [60]. In clinical practice this facilitates the same outcome with a smaller light fluence, further reducing the damage to healthy tissue.

Combining a bioprecursor (prodrug), coumarin and triphenylphosphonium then incorporating them onto carbon dots allows mitochondria to be targeted and the achievement of highly localised PDT with limited damage to surrounding cells [61]. Omitting the incubation period may lend itself to specific settings and applications. Treatment of leg ulcers and wounds with methylene blue and an 810 nm diode laser (fluence 60 J/cm²) did not require any incubation time and was shown to be much more successful than just using the laser; two-thirds of ulcers showed partial improvement, while 83% of split skin sites showed a very good response [62]. Similar chemical and physical parameters and a

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**Table 1** Photosensitisers used in antimicrobial PDT studies by a range of methods

| Photosensitiser       | First author          | Year | Type of study | Absorption | Attributes                                                                 |
|-----------------------|-----------------------|------|---------------|------------|---------------------------------------------------------------------------|
| Porphyrins            | Merchat [101]         | 1996 | Animal lab    | 610-630 nm | Cationic versions are suited to killing of bacteria                       |
| Pthalocyanines        | Ng [102]              | 2014 | Clinical      | 670-700 nm | Absorbs at low energies. High production of ROS and low skin toxicity in ambient light support their topical use |
| 5-Aminovulinic acid   | Ibbotson [103]        | 2002 | Clinical      | 503-628 nm | Rapid action reduces the risk of photosensitivity                         |
| Chlorins              | De Annunzio [104]     | 2019 | Clinical      | 650-660 nm | Has a high quantum yield of singlet oxygen                               |
| Xanthenes             | Yin [105]             | 2015 | Animal lab    | 532 nm     | Kills viruses, bacteria and protozoa                                     |
| Phenothiazines        | Wison and Mia [106]   | 1993 | Biological lab | 625 nm, 656 nm | Kills both Gram-positive and Gram-negative bacteria and some fungi       |
| Triarylmethanes       | Noimark [107]         | 2016 | Theoretical and materials lab | 700 nm | Kills both Gram-positive and Gram-negative bacteria                        |
| Phyto-therapeutic agents | Nardini [108]        | 2019 | Dental lab    | 405 nm | Significant reduction of planktonic and biofilm manifestations of E. faecalis in Bovine dentin samples |
| Cyanines              | Delaey [109]          | 2000 | Biological lab | 545 nm-824 nm | High degree of photosensitisation in vitro                               |
| Fullerenes            | Tegos [110]           | 2005 | Chemical lab  | Visible light | Kills Gram-positive bacteria, Gram-negative bacteria, and fungi          |
| Vitamin B derivatives | Baier [111] Maish [112] | 2006 | Biological lab | UV | Greatly reduces multi-resistant bacteria                                  |
| Curcumin              | Qiong-Qiong Yang [113]| 2020 | Biological lab | 470 nm | Destroyed Staphylococcus aureus and prevented it’s regrowth               |
| Curcumin              | Qiong-Qiong Yang [113]| 2020 | Animal lab    | 470 nm     | Reduced Streptococcus mutans in dental samples                            |
minimal incubation period (15 min) were used by Morley and co-authors [63] in a Phase IIa placebo-controlled Randomised controlled trial (RCT). They demonstrated complete clearance of half (four out of eight) of the treated leg ulcers by 3 months, with less conclusive results on a cohort with diabetic foot ulcers (DFU’s). A development of this DFU work [68] recommended PDT to target gram-positive cocci in cellulitis therapy. The surface area of leg ulcers was reduced by three in those receiving ten high-fluence treatments of ALA PDT, compared to a halving in size of placebo groups lesions [64].

As the total annual cost of diabetic foot ulcer complications in the UK is £252 million [65], the ability to eradicate a range of bacterial species across large areas and volumes of tissue is paramount. In the longer term, prevention of DFU’s is desirable and a recent systematic review [66] identified bespoke orthotics, antifungal nail lacquer and elastic compression stockings as appropriate methods in those at risk. A 2017 International consensus statement on the treatment of DFU’s [67] appealed for strategies appropriate to a resource-limited setting. Daylight PDT depends only the availability of a characterised photosensitising ointment, opaque dressings and knowledge of the relationship between real-time solar irradiance and fluence (J/cm²) given a geographical location.

AMPS are cationic and combat infection through their direct microbicidal properties and/or by influencing the host’s immune responses [68]. The former property targets the cytoplasmic membrane or the peptidoglycan cell wall both of which are robust structures that do not change easily meaning resistance does not develop. Identifying and harvesting naturally occurring AMPs is labour intensive, however, equipment and protocols have now been developed to synthesise them artificially, [69, 70] and peptide libraries of the increasing number of known organic and synthetic versions also emerging [71]. DRAMP 2.0 is perhaps the most detailed database which identifies just 76 AMPs in clinical use (less than 1% of the total) [72] and only seven AMPS with FDA approval [27]. These small numbers imply that both scientific and administrative constraints exist on the transition from the laboratory to clinical practice- and more research could be focused on these areas.

In vitro studies have demonstrated that commonly prescribed antidepressants Citalopram and Venlafaxine enhance the effect of antibiotics [73]. Moreover, Citalopram increased susceptibility of Cefixime-resistant Escherichia coli and Cloxacillin-resistant Pseudomonas aeruginosa when used alongside these antibiotics. Likewise, Venlafaxine increased the susceptibility of resistant P. aeruginosa to the same drugs. The underlying mechanism is thought to be blocking of de novo efflux pumps formed during the resistance process [73]. However, this does not apply to all SSRI and SNRI drugs; fluoxetine, has been shown to increase the mutation frequency of E. coli to a series of antibiotics [74]. There are many other drugs and supplements thought to inhibit the effect of antibiotics and ultimately exacerbate AMR [79] and consideration of these specific interactions during prescribing is a necessary step in antimicrobial stewardship.

The original 2002 European Guidelines for topical PDT [75] provided a review of its historical use, concluding that both coherent and non-coherent light sources were suitable and acknowledging 5-ALA as the most prevalent photosensitiser. It also highlighted the antimicrobial applications of PDT for acne and warts. By 2008 [76] Acne, warts and Cutaneous Leishmaniasis (CL) were given a B strength of recommendation for treatment with PDT, secondary to first-class evidence according to the GRADE system [77] (Tables 2, 3).

Table 2 Grading used for the quality of evidence used for clinical recommendations

| Quality of Evidence | Symbol | Letter |
|---------------------|--------|--------|
| High                | 🙌🙌🙌🙌 | A      |
| Moderate            | 🙌🙌🙌 | B      |
| Low                 | 🙌🙌 | C      |
| Very Low            | 🙌 | D      |

Table 3 Terminology and symbols used to communicate the strength of a clinical recommendation

| Strength of Recommendation | Symbol | Number | Letter |
|-----------------------------|--------|--------|--------|
| Strong for Intervention     | 1      | A      |
| Weak for Intervention       | ?      | 2      | B      |
| Weak against Intervention   | ?      | 2      | B      |
| Strong against Intervention | 1      | A      |
were also mentioned as they had top quality evidence with a ‘B’ strength of recommendation. For warts, ALA followed by a pulsed dye laser or LED source gave clearance rates of up to 100% [80]. In CL, ALA with red light illumination was found to be effective, with no relapses at 6 months [81]. Finally, the use of PDT for the fungal infection Onychomycosis was introduced cautiously.

In the 2019 update of the European guidelines for topical PDT [82], Acne, CL, Onychomycosis and refractory warts all achieved a B strength of recommendation given high-quality evidence. Similar outcomes for ALA-PDT and MAL-PDT were reported for acne, however, MAL had fewer side effects [83]. Blue and red-light illumination were reported to provide similar results, despite the earlier assertion that longer wavelengths (red) are more penetrating, providing permanent results. Daylight PDT was also successful for treating acne, when fractional laser-assisted [84]. For warts, evidence of excellent results using ALA was reported [85] with low recurrence rates relative to CO2 laser treatment [86]. New data for the Leishmania major and Leishmania tropica species causing CL revealed optimal results using multiple red-light PDT treatments with high fluences (up to 100 J/cm²) [87], with repeat daylight PDT proving reasonably effective [88]. For Onychomycosis, methylene blue PDT was very effective, especially with prior abrasion of the nail with fluniconazole [89].

The British Association of Dermatologists (BAD)/British Photodermatology Group (BPG) published their recommendations in 2018 based on the available evidence, as well as consensus and specialist experience [90]. The four pertinent recommendations of the British group were: (1) Consider PDT for CL, particularly in cosmetically sensitive sites; (2) Consider daylight PDT for CL, bearing in mind that several treatments may be required; (3) Consider PDT as a treatment option for recalcitrant viral warts; (4) Do not offer PDT as a treatment option for fungal infections. Notably, this guideline does not mention Acne in its recommendations, and it concurs with the contemporaneous European guideline on viral warts, and essentially for CL. Both documents align on the use of serial daylight PDT for CL and a less onerous approach is also likely to be popular with patients.

The first-ever UK NICE clinical guideline on the management of Acne Vulgaris will be published in 2021 and lists topical medicines and antibiotics in various combinations as first and second-line treatments, with referral to a consultant dermatologist and the use of oral isotretinoin and prednisolone as third-line treatments [91]. There is a risk that the C. acnes and commensal microflora of patients using topical antibiotics, and their close contacts, will develop antibiotic resistance, however, concurrent use of topical retinoids or Benzoyl peroxide negate this [92, 93]. PDT is highlighted for consideration in adults with moderate to severe acne if other treatments are contraindicated, ineffective or poorly tolerated. Similarly, it is not contraindicated for children. Pertinently to this review, one of its recommendations for research is the investigation of light devices in the treatment of acne vulgaris and its persistent scarring.

There are no active NICE guidelines on CL, Onychomycosis, warts, Leg ulcers (LU), or diabetic foot ulcers (DFU). However NICE technology appraisal of Urgostart dressings mentions their suitability for both types of ulcer [94] with antibiotics only necessary if the lesion becomes clinically infected. Offloading is the reduction, redistribution or removal of detrimental forces applied to the foot [95] and is a primary treatment for foot ulcers alongside control of ischaemia and wound debridement. Technology appraisal of Ambulight PDT for small non-melanoma skin cancer supports its use and highlights that the relatively low irradiance is less painful than conventional PDT [96]. While it is more expensive to implement, it would certainly have an antimicrobial application in circumstances where conventional PDT is unavailable and daylight PDT is inappropriate. Clinical trials would establish the optimum doses and treatment regimens for different types of ulcer (Table 4).

Table three ranks the outcome of PDT in Clinical Antimicrobial PDT studies. As this parameter was often reported qualitatively, I have shown how I converted each outcome into a percentage and acknowledge the subjectivity involved. It can be surmised that 100% eradication of warts and acne is possible, and very good results for leg ulcers is achievable. Porphyrin or very long incubation periods after ALA application were specifically beneficial for warts. In acne, the best results were achieved with ALA and a very small light fluence. Leg Ulcers responded to the combination of methylene blue and infrared light with standard fluence and incubation; but when the latter was reduced, results were poor. CL was consistently improved rather than resolved completely and this applied to a range of photosensitiser/λ combinations.

The overall results for aPDT are more variable than those seen for skin cancers [40, 43], where an average efficacy of 82% was found. Cancer research has a long and relatively well-funded history with more focus on the optimal technical combinations and so further methodological research in aPDT may yield improved clinical results. The variation in findings for aPDT is echoed by the subset of clinical applications unrelated to cancer or microbes ([45, 46, 48–50], table Ibbotson).

The long-term impact of the clinical guidelines discussed here and the broader WHO strategy for reducing antimicrobial resistance [97] can be monitored on antibiotic footprint. net and eucast.org. The former shows antibiotic use across countries and industries, and the latter lists minimum inhibitory concentrations (MICs) of a range of antibiotics for the eradication of a variety of microbes. Increasing MIC values for a specific drug-pathogen combination indicates that
resistance is developing over time and so maintenance may be the desirable outcome.

So, in conclusion, combinations of treatments for microbial infection will optimise outcomes in the future and more clinical trials are necessary to demonstrate the ideal mix and delivery methods of agents and illumination for specific conditions and patient cohorts. Nanotheranostics will be subject to broad clinical evaluation and may include PDT for antimicrobial indications. Reported uses of this emergent technology include: the delivery of AMPs [98] and antibiotics [31]; with adjunct illumination to modulate antibiotic function or monitor progress in bacterial eradication [12]; simultaneous PDT, PTT and bioluminescence [99]; the management of sepsis [100]. Conventional PDT will undoubtedly play a part given its large evidence base and existing healthcare facilities and infrastructure—it may be the only treatment necessary for some cases of Acne vulgaris and related scarring. Daylight PDT and the use of ambulatory devices could become more popular in regions where resources are limited, with a broader scope than just CL and Acne Vulgaris—subject to high-quality evidence. In theory, the resistance of microbes to antibiotics is reversible, and in practice it is possible that new resistance could at least be halted by the use of supplementary drugs. Antibiotics are therefore unlikely to become obsolete.

### Table 4 Antimicrobial applications of PDT and their clinical efficacy

| References | Pathology          | Photosensitiser | Light            | Additional facilitation | Reported efficacy (%) | Estimated efficacy (%) |
|------------|--------------------|-----------------|------------------|-------------------------|-----------------------|------------------------|
| [104]      | Viral warts        | Porphyrin       | Red              | –                       | 100                   | 100                    |
| [103]      | Recalcitrant viral warts | ALA           | Broadband visible | Quadruple incubation period | 100                   | 100                    |
| [103]      | Acne               | ALA             | Broadband visible | Small fluence           | 100                   | 100                    |
| [103]      | Acne               | ALA             | Red              | Very small fluence      | 100                   | 100                    |
| 61         | Leg ulcers         | Methylene blue  | Infrared         | –                       | 83                    | 83                     |
| [103]      | Recalcitrant viral warts | ALA           | Broadband visible | Large fluence           | 75                    | 75                     |
| [103]      | Recalcitrant viral warts | ALA           | Broadband visible | –                       | 73                    | 73                     |
| 75b        | Warts              | ALA             | Broadband        | –                       | 58                    | 58                     |
| [103]      | Recalcitrant viral warts | ALA           | Broadband visible | Prior paring to blood vessels, Large fluence | 56                    | 56                     |
| 75c        | Warts              | ALA             | Broadband        | Reduced incubation period | 56                    | 56                     |
| 62a        | Leg ulcers         | Methylene Blue  | Infrared         | Reduced incubation period | 50                    | 50                     |
| [104]      | Cutaneous leishmaniasis | Porphyrin     | Red              | –                       | Reduced parasitic load | 50                     |
| [104]      | Cutaneous leishmaniasis | Phthalocyanine | Red              | –                       | Reduced parasitic load | 50                     |
| [104]      | Cutaneous leishmaniasis | Chlorine      | Blue             | –                       | Reduced parasitic load | 50                     |
| [104]      | Acne               | Porphyrin       | Red              | –                       | Reduced number of lesions | 50                     |
| Acne       | Chlorine           | Red             | –                | Reduced microbial load  | 50                     |
| 75a        | Acne               | ALA             | Broadband visible | Large fluence           | Clinical improvement  | 50                     |
| [103]      | Recalcitrant viral warts | ALA           | Red              | –                       | All improved          | 50                     |
| 63         | Cellulitis         | ALA             | Red              | –                       | 42                    | 42                     |
| [103]      | Recalcitrant viral warts | ALA           | Blue             | –                       | 40                    | 40                     |
| 62b        | Diabetic foot ulcers | Methylene blue  | 810 nm           | Reduced incubation period | Inconclusive          | 0                      |

Table 4: Antimicrobial applications of PDT and their clinical efficacy. Typical technical parameters are a 4 h incubation period after photosensitiser application and a light fluence of 37 J/cm²; significant variations from this are noted.
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Data availability As there was no data collected for this review, data cannot be made available.

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

Declarations

Conflict of interest The author has no conflicts of interest to disclose.

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

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

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

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Authors and Affiliations

Alison M. Mackay1,2,3

1 Division of Musculoskeletal and Dermatological Sciences, University of Manchester, Manchester, UK
2 Clinical Engineering, Salford Royal Foundation Trust, Salford, UK
3 Photobiology, Dermatology Centre, Salford Royal Foundation Trust, Salford, UK