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Photodynamic Therapy for Infections: Clinical Applications

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Abstract

Background and Objective—Photodynamic therapy (PDT) was discovered over 100 years ago by its ability to kill various microorganisms when the appropriate dye and light were combined in the presence of oxygen. However it is only in relatively recent times that PDT has been studied as a treatment for various types of localized infections. This resurgence of interest has been partly motivated by the alarming increase in drug resistance amongst bacteria and other pathogens. This review will focus on the clinical applications of antimicrobial PDT.

Study Design/Materials and Methods—The published peer-reviewed literature was reviewed between 1960 and 2011.

Results—The basics of antimicrobial PDT are discussed. Clinical applications of antimicrobial PDT to localized viral infections caused by herpes and papilloma viruses, and nonviral dermatological infections such as acne and other yeast, fungal and bacterial skin infections are covered. PDT has been used to treat bacterial infections in brain abscesses and non-healing ulcers. PDT for dental infections including periodontitis and endodontics has been well studied. PDT has also been used for cutaneous Leishmaniasis. Clinical trials of PDT and blue light alone therapy for gastric *Helicobacter pylori* infection are also covered.

Conclusion—As yet clinical PDT for infections has been mainly in the field of dermatology using 5-aminolevulanic acid and in dentistry using phenothiazinium dyes. We expect more to see applications of PDT to more challenging infections using advanced antimicrobial photosensitizers targeted to microbial cells in the years to come.

Keywords

photodynamic therapy; infectious disease; amimolevulinic acid; phenothiazinium dye; bacteria; fungus; virus; parasite

INTRODUCTION

Photodynamic therapy (PDT) is a technique that utilizes reactive oxygen species (ROS) produced by a non-toxic dye or photosensitizer (PS) molecule in the presence of low intensity visible light to kill mammalian or microbial cells. The photochemical process involves exciting the PS molecule with visible light of the appropriate wavelength matched

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to an absorption band. The PS molecule goes to the first excited singlet state which may then undergo intersystem crossing to a slightly lower energy but longer-lived triplet state. The long-lived triplet state further reacts via type I or/and type II photochemical pathways to produce superoxide, hydroxyl radicals [1] and singlet oxygen [2] respectively (Fig. 1), leading to cytotoxicity.

Though PDT was discovered in the field of microbiology over 100 years ago, it has been mostly applied for cancer treatment and ophthalmology. Its application in the field of infectious diseases underwent a major setback with discovery of antibiotics in 1940s. This discovery revolutionized the treatment of infectious diseases caused by pathogenic bacteria and in due course antifungal, antiprotozoal, anthelmintic, and antimalarial compounds were available. The initial studies of antimicrobial PDT, in the 1970s, involved clinical treatment of viral lesions [3] but this practice ceased when a paper in New England Journal of Medicine [4] claimed that the procedure was ineffective. Also concern was raised about the treatment being a possible cause of cancer [5]. Thus, in spite of a 100 years of discovery, the progress in the field of antimicrobial PDT has been rather slow. But with the recent rise in antibiotic resistance throughout the world, there has been renewed interest in alternative antimicrobial therapies. Antimicrobial PDT also known as photodynamic inactivation (PDI), lethal photosensitization, photoactivated disinfection (PAD) or photodynamic antimicrobial chemotherapy (PACT) represents an alternative treatment for drug resistant pathogens and has made a comeback as a possible approach to treat multidrug resistant infections. Drug resistant bacteria can be effectively eliminated by PDT [6] and as of yet there are no reports of microbes becoming resistant to PDI despite numerous attempts to induce resistance by repeated cycles of semi-lethal PDT and microbial regrowth [7].

Antimicrobial PDT with a wide range of PS molecules is more effective in inactivating Gram-positive as compared to Gram negative bacteria. The differential susceptibility to PDT arises due to differences in the cell wall structures of these two groups. In Gram positive bacteria, the cytoplasmic membrane is surrounded by a relatively porous layer of peptidoglycan and lipotechoic acid that allows the PS to cross [8]. The cell envelope of Gram negative bacteria consists of an inner cytoplasmic membrane and an outer membrane that are separated by the peptidoglycan containing periplasm (Fig. 2). The outer membrane forms an effective permeability barrier and restricts binding and penetration of many PS [9]. The fungal cell wall is made up of a thick layer of beta glucan and chitin and also provides a permeability barrier, intermediate between Gram positive and Gram negative bacteria. To overcome this permeability barrier, several approaches have been applied. Use of PS in combination with a permeabilizing agent such as polymyxin nonapeptide [10] or EDTA [11] made PDT treatment effective against Gram negative bacteria. Imparting positive charge to PS can also produce broad spectrum PS that could inactivate all classes of microorganisms: Gram-positive, Gram-negative bacteria [12], fungi [13], viruses [14], parasites [15] and even highly resistant life forms such as bacterial spores [16] and the cystic stage of Acanthamoeba [17]. The PS that are commonly used in antimicrobial therapy in vitro include a very wide range of compounds most of which are cationic [18]. Considerable effort has been put into optimizing many of these compounds in areas such as selectivity for microbial cells over host mammalian cells [19], maximizing absorption in far-red and near infrared regions of the spectrum [20] and reducing photobleaching [21]. These have proven to be very effective in vitro and in vivo in animal models of infection, but most of these PS are yet to be tested in the clinical trials. The range of PS that has been used in clinical studies is more restricted in variety. Phenothiazinium dyes (methylene blue, toluidine blue, and PP904); porphyrins including ALA–PPIX and hematoporphyrin derivatives, neutral red, and a conjugate between chlorin(e6) and polyethylenimine have been used (see Fig. 3 for chemical structures).

Many clinical application of PDT for infections involve topical application of the porphyrin precursor amino acid, 5-aminolevulinic acid or the ALA-methyl ester known as methyl aminolevulinate, MAL. ALA application leads to accumulation of the PS, protoporphyrin IX in cells having heme biosynthesis enzymes (both microbial and mammalian) as shown in Figure 4. There are some difference between these two sets of pathways particularly in the early stages where bacteria use glutamate semi aldehyde to form ALA, while mammalian cells use glycine and succinyl co-enzyme A but both cells accumulate an excess of PPIX when ALA is exogenously supplied. It should be noted that it is presently uncertain to what extent the success gained by treating fungal and bacterial infections with PDT mediated by ALA relies on porphyrin synthesis by host cells or by microbial cells. In the case of viral infections and Leishmaniasis it is clearly the host cells because both viruses and Leishmania parasites are incapable of porphyrin synthesis.

ALA–PDT is clinically used for acne, Leishmaniasis and other skin infections including those caused by fungi. Other widespread clinical applications of antimicrobial PDT are in viral lesions and dentistry. Also clinical trials involving gastric *Helicobacter pylori* infection, infected leg ulcer and brain abscesses have been conducted. Figure 5 schematically illustrates the range of clinical applications of PDT for infections that are also listed in Table 1.

PDT OF VIRAL LESIONS

Many of the initial clinical studies of PDT in infectious diseases were directed towards viral lesions. Topical PDT was commonly tested to treat herpes simplex lesions. Herpes keratitis was healed by proflavine photodynamic viral inactivation [22]. Topical application of methylene blue and neutral red eradicated genital herpes but could not prevent the recurrence [23]. However in several other studies, photoinactivation of herpes virus with neutral red was found to be ineffective [4,24]. In addition to this there were apprehensions about the possible carcinogenic effect of this therapy [5].

In recent years several clinical trials of PDT have been conducted against viral infections, especially human papilloma virus (HPV). Systemic and topical PDT in several anatomic sites has been used to treat papillomatosis caused by HPV. It's a potentially life threatening recurrent respiratory tract disease affecting both children and adults. Systemic treatment of 48 patients with 50 J of 630 nm laser light 48 hours after dihematoporphyrin ether (4.25 mg/kg) significantly decreased papilloma growth rate compared to control patients. A follow up for 3 years of subset of patients confirmed that the improvement was maintained [25]. Abramson et al. [26] and Bujia et al. [27] reported similar results. An interesting case of a 65-year woman, who suffered from epidermodysplasia verruciformis (wart like lesions) for more than 45 years, was reported by Karrer et al. [28]. The lesions were irradiated with 580–740 nm light (160 mW, 160 J/cm^2) 6 hours after application of 20% ALA ointment. There was blistering and crusting of lesions which healed completely within 2–3 weeks without scarring and cosmetic results was excellent. A few lesions recurred 12 months after PDT. There is no permanent cure for epidermodysplasia verruciformis but topical PDT may result in better control of HPV-induced lesion. ALA–PDT has been used to treat cutaneous warts also known as verrucae vulgaris or verrucae plana, caused by HPV. Forty-two of the 48 plantar warts in 31 patients who received ALA (mean incubation time 6.8 hours and mean treatment time 18.7 minutes per wart) showed complete response and no significant side effects post-operation. The total clearance seems to be related to the size of the warts, age of the patient and mean treatment time [29]. ALA–PDT of 250 recalcitrant warts in 30 patients with white light was found to be better than red or blue light and also standard cryotherapy [30]. Seventy three percent of warts treated with white light thrice were completely healed, 71% after one application of white light, 42% after 3X red light, 23% after 3X blue light and

20% after cryotherapy treatments. No scars or recurrences in patients completely responding to ALA–PDT treatment was observed after a year of follow up. ALA–PDT was also found to be superior to placebo-PDT when both wart area and number of vanishing warts were considered [31]. The same group also studied the pain induced by ALA–PDT of warts and found the treatment was painful and 17% of patients had to receive pharmacological pain relief [32]. Application of 20% ALA–PDT on three patients with recalcitrant facial warts for one session achieved excellent results [33]. Besides HPV induced skin viral lesions, skin infections like molluscum contagiosum [34,35] and the ones caused by herpes simplex can be successfully treated [36]. It has been suggested that the treatment of HPV infections by PDT is because of its anti-inflammatory and antiproliferative effects in the lesions [36].

Condyloma accuminata are the genital warts caused by HPV. In women, HPV can also infect the uterine cervix and may lead to development of cervical intraepithelial neoplasia (CIN) and cervical cancer depending on the virus subtype. PDT with polyhematoporphyrin ether/ester 2 mg/kg IV for applied for 60 hours and irradiated with 630 nm YAG-OPO laser improved cytological measures when treating CIN and also eradicated HPV [37]. Similar results were obtained when infection was photoinactivated with photolon [38] and 5-ALA [39]. Topical application of 5-ALA PDT also successfully treated 13 of the 14 cases of anogenital condyloma accuminata [40]. Topical ALA or MAL–PDT has also been used to treat condyloma in the vulva, vagina, and penis wherein selective accumulation of PPIX was demonstrated in the lesions [41,42]. Chen et al. [43] compared ALA–PDT with CO_2 laser vaporization for the treatment of condylomata. After one treatment with CO_2 laser and ALA–PDT (20% ALA solution under occlusive dressing for 3 hours followed by irradiation with He–Ne laser at 100 J/cm^2), the complete removal rate was 95% in ALA–PDT and 100% in control group. But the recurrence rate was significantly lower (6.3%) as compared to control group (19.1%). Moreover the proportion of patients with adverse effects in ALA–PDT group was also significantly lower than the CO_2 laser group. However Szeimies et al. [44] did not find any difference in recurrence rates when ALA–PDT was combined with CO_2 laser. Topical ALA and red light (630 nm) was used to treat genital condylomata in nine men who had at least one unsuccessful conventional treatment. Complete cure was achieved in three patients, one of whom experienced a relapse while three patients showed partial responses and three showed no response [45]. Treatment of 164 patients with intraurethral condylomata with topical ALA followed by intraurethral light delivery led to a response rate of 95% and recurrence rate was 5% after 6–24 months of follow up [46].

The response of the genital lesions to PDT treatment may be dependent on the immune response as indicated by the study of Abdel-Hady et al. [47]. They used ALA–PDT to treat high-grade vulval intraepithelial neoplasia (VIN 2–3) lesions but observed a short term response in only one third of the cases. Unifocal lesions were found more responsive than multifocal and pigmented lesions. HPV infection, HLS expression, and immune infiltrating cells in VIN biopsies from responders and nonresponders were measured. There was greater likelihood of HPV positivity associated with a lack of response to VIN to PDT, and VIN nonresponders were more likely to show HLA class I loss compared with responders. There was significant increase of CD8 infiltration in post-treatment VIN responders compared with nonresponders. High risk HPV infection and lack of cell-mediated immunity may play a role in the observed poor response of lower genital lesions to topical PDT.

There was an interesting study [47] in which PDT mediated by benzoporphyrin derivative was used in a photopheresis technique in ten HIV-1 infected patients. Photopheresis involved removing a blood sample (300 mL), isolating the leukocyte-rich fraction (buffy coat), incubating it with BPD for 30 minutes, exposing it to UVA light in a specialized photopheresis apparatus and re-infusing it back to the patient. A course of treatment was initially 3 monthly pheresis sessions followed by 6 pheresis sessions every 2 weeks for a

total of 9 treatments. Subsequently, the protocol was amended such that new enrollees were scheduled to receive pheresis every 2 weeks for 12 months (24 phereses). Three patients who had rapidly rising viral loads prior to initiating therapy stabilized. Two had a sustained greater than 0.5 log decrement and 5 had stable plasma viral loads (less than a 0.5 log increment or decrement) with varied effects on absolute CD4 and CD8 positive lymphocyte counts. One patient achieved a greater than 1 log decrement in HIV-1 plasma viral load and undetectable in vivo cell-free and cell-associated HIV-1 infectivity with an increased in vitro lymphocyte mitogen stimulation index.

PDT FOR NONVIRAL DERMATOLOGICAL INFECTIONS

Acne

Acne vulgaris, the most common dermatological disorder, is a multifactorial disease and defined as a disorder of the sebaceous glands wherein the sebaceous glands are obstructed leading to proliferation of bacteria in those glands. The predominant bacterium is *Propionibacterium acnes* which naturally produces porphyrins mainly protoporphyrin IX and coproporphyrin III [48], thus eliminating the need of applying any PS and using only a light source to treat the acne. Several studies have shown a mild to moderate inflammatory acne vulgaris on all skin types without any adverse effects [49–51]. Other than blue light, green [52], and yellow [53] light have also proved effective in treatment of mild to moderate acne vulgaris lesions. Moreover Ramstad et al. [54] showed that even more porphyrins were accumulated in the presence of ALA or MAL especially if the temperature was raised. ALA and MAL–PDT have proved to be effective and safe way of treating acne [55,56]. The first reported clinical trial utilizing ALA in acne vulgaris treatment was by Hongcharu et al. [57] using a 550–570 nm broad band light source. Since then there have been a number of clinical trials that successfully treated acne with ALA–PDT with different light sources and different regimens [58–61]. PDT with intralesional injection of ALA showed a definite statistical superiority in raising specificity of treatment and shortening the incubation time compared to conventional ALA–PDT [62]. A recent study by An et al. [63] conducted PDT with liposome encapsulated 0.5% ALA in 13 Korean subjects and found it to be effective and without any side effects. MAL–PDT is also an effective way to treat inflammatory acne [64–66] and there seems to be no significant differences in the response rate between ALA–PDT and MAL–PDT [67]. Taylor and Gonzalez [68] reported that topical short-contact application of ALA or MAL and illumination with a noncoherent light source at 2–4 weeks intervals for a total of two to four treatment produced greatest clinical effects. Use of other PS such as indocyanine green dye (in combination with NIR diode laser—803 or 809 nm) [69] and chlorophyll [70] to treat acne have also been demonstrated. The clinical trials and case reports of PDT for acne has been critically analyzed in a review by Sakamoto and Anderson [71].

OTHER DERMATOLOGIC INFECTIONS

Rosacea is a chronic condition characterized by facial erythema and has been associated with various infections. MAL–PDT treatment in patients with rosacea using red light achieved good results in 10 out of 17 patients and fair results in another four patients [72]. However there were no changes in bacterial flora of skin after MAL–PDT. Katz and Patel [73] treated severe rosacea in a 45-year woman with six sessions of ALA–PDT given at 2-week intervals. An improvement was evident and there were no flares 1 month after the final treatment.

Darras-Vercambre et al. [74] reported the first cases of PDT of erythrasma, a superficial cutaneous infection caused by *Corynebacterium minutissimum* that exhibits red fluorescence under Woods light. Illumination (80 J/cm^2) by red light (broad band, peak at 635 nm)

without exogenous photosensitizing molecules achieved a complete recovery for some patients.

Wiegell et al. [75] cured a patient with a skin infection caused by *Mycobacterium marinum* [76] by first treating the lesion with 10 weekly 7.8-J/cm^2 doses of blue light and then using ALA–PDT on the remaining lesions once a week for 3 weeks using illumination with 37-J/cm^2 doses of red light.

Calzavara-Pinton et al. [77] applied 20% ALA preparation in Eucerin cream under an occlusive dressing to skin lesions of interdigital mycosis of the feet caused by Candia or Trichophyton species followed by irradiation of 75 J/cm^2 of broad band red light. Clinical and microbiological recovery were seen in six out of nine patients after one (four patients) or four (two patients) treatments. A similar study was carried out by Sotiriou et al. [78] on 10 patients with interdigital tinea pedis caused by Trichophyton using ALA–PDT. Six out of 10 achieved mycological cure after 1–3 treatments but 3 had recurred at 8-week follow up. The same group [79] treated 10 patients with tinea cruris (also known as ringworm of the groin or jock itch) caused by *T. rubrum* with ALA–PDT. Eight out of 10 patients achieved mycological cure and 4 of these remained cured at 8 weeks. Toenail onychomycosis is another fungal infection caused by Trichophyton species. Watanabe et al. [80] treated two patients by applying a 20% urea ointment to the diseased nail surface and covered with a piece of plastic film wrap for 10 hours. Then, a 20% solution of ALA methyl ester in aqueous cream was applied to the treated nails, sealed with a piece of plastic film wrap and covered with aluminum foil to shut out the light for 5 hours. Before PDT, ALA-induced protoporphyrin IX fluorescence was confirmed at the base of the nail and at the periphery of the onychomycosis lesion. The nails including the proximal and lateral nail folds, were irradiated both horizontally and vertically with pulsed laser light at a wavelength of 630 nm at 100 J/cm^2 using an excimer-dye laser. The treatment was repeated 6–7 times at weekly intervals leading to mycological cure in treated nails (but not control nails) and no recurrence was seen at 3–6 months follow ups. Several other reports of ALA–PDT for onychomycosis have now appeared [81–83] leading to the hypothesis that PDT may be a viable alternative approach for this intractable condition.

Malassezia folliculitis is a skin disorder caused by yeast specifically, *Malassezia furfur*. The oral antifungal medications commonly used for this disease have several adverse effects and there are instances of infection relapse thus necessitating a need for alternative treatment. Lee et al. [84] tested ALA–PDT and 630 nm laser (37 J/cm^2) in six Korean patients with recalcitrant Malassezia folliculitis. The inflammatory lesions had decreased and improved obviously in four patients, had improved slightly in one patient, and had not improved in one patient after three sessions of MAL–PDT. Pityriasis versicolor is another skin disease caused by Malassezia yeasts. Kim and Kim [85] treated a patient with the disease affecting the axillae with ALA–PDT mediated by red light (70–100 J/cm^2) twice (2 weeks apart) and obtained complete clearance.

PDT FOR LOCALIZED BACTERIAL INFECTIONS

Not many clinical trials of PDT in localized bacterial infections have been reported. In one study, treatment of localized bacterial infections by topical administration of PS was reported [86]. They treated five patients with brain abscesses after craniotomy and surgical drainage by introducing hematoporphyrin into the abscess bed and illuminating 5 min afterwards, producing a positive clinical response. PDT of nonhealing leg ulcers infected with bacteria mediated by a new phenothiazinium derivative (PP904) was carried out by a UK based company, Photopharmica. Improved would healing and microbial reductions were found but these data have so far only been presented at conferences [87]. Clayton and

Harrison [88] reported a significant improvement in the healing of an infected leg ulcer of a 72-year-old woman who was given topical ALA–PDT twice weekly over 4 weeks but it was not clear how much of this improvement was due to the antimicrobial effect.

PDT OF DENTAL INFECTIONS

Applications of antimicrobial PDT in oral infections in the field of dentistry is one of the most widespread today. PDT for dental infectious represents the largest growth area of clinical antimicrobial PDT. This is because three companies, Ondine Biomedical, Vancouver, Canada, Helbo Photodynamic Systems, Weis, Austria, and Denfotex Ltd, Inverkeithing, UK, are actively involved in clinical trials and are marketing therapies which are still relatively unknown among the general medical profession.

Two of the most common bacterial diseases afflicting humans are dental caries and periodontal diseases resulting from build-up of plaque biofilms on the teeth and soft tissues of the mouth. Periodontitis is accompanied with inflammation of connective tissue in the dental pocket and resorption of alveolar bone. In PDT of periodontitis the photosensitizer is usually injected into the dental pocket followed soon after by light delivery into the dental pocket using a narrow fiber optic tip. de Oliveira et al. [89] compared PDT with toluidine blue O (TBO) and 660-nm laser with the scaling and rooting planning (SRP) using manual instruments in 10 patients with aggressive periodontitis. Both these nonsurgical treatments had similar clinical effects. The same group studied the cytokine values which are of considerable value when studying the disease course during treatment [90]. They investigated cytokine levels (tumor necrosis factor-alpha and receptor activator nuclear factor-kappa B ligand) in the gingival crevicular fluid (GCF) of 10 patients with aggressive periodontitis, after treatment with PDT or SRP. Both treatment, SRP and PDT, had similar effects on the cytokine levels in patients with aggressive periodontitis. Additional application of a single application of PDT to SRP resulted in significantly higher reduction of bleeding scores than using SRP alone [91,92]. Braun et al. [93] reported that in patients with chronic periodontitis, clinical outcomes of conventional subgingival debridement can be improved by adjunctive TBO–PDT and 670 nm laser (100 mW/cm^2). PDT administered after SRP treatment in patients with *Fusobacterium nucleatum* infected periodontitis reduced periodontal inflammatory symptom and successfully treated *F. nucleatum* infection [94]. Ruhling et al. [95] compared PDT using TBO with a 635-nm laser with ultrasonic debridement in persistent pockets of maintenance patients and found that both therapies performed similarly. Ge et al. [96] used methylene blue and 670-nm laser to perform PDT after SRP and compared this approach with SRP alone. There was less bleeding on probing in the PDT group. Lui et al. [97] combined low level laser therapy with PDT with the aim of reducing the inflammatory effect caused by the periodontal therapy.

Another application of antimicrobial PDT in dentistry is in the sterilization of endodontic root canals in patients who are being treated for necrotic pulp and periapical lesions. PDT can be combined with the usual mechanical debridement and chemical antimicrobials such as hypochlorite and hydrogen peroxide. This approach was found to be successful by Garcez et al. [98] who reported that combination of PDT using a conjugate between polyethylenimine and chlorin(e6) [99] illuminated with 660-nm laser and standard endodontic treatment leads to an enhanced decrease in bacterial load determined by successive sampling in a clinical trial carried out in 20 teeth Similar results were reported by Pinheiro et al. [100] who used a TBO + urea peroxide preparation and red light in addition to mechanical instrumentation to sterilize root canals in children with deciduous teeth with necrotic pulps. There was a reduction of 82.59% viable bacteria after instrumentation and after PDT the reduction was 98.37%.

PDT OF LEISHMANIASIS

Leishmaniasis is a disease caused by protozoan parasite transmitted by bite of certain species of sand fly. Cutaneous Leishmaniasis is the most common form of Leishmaniasis. A weekly treatment of 10% ALA PDT with red light (630 nm, 100 J/cm^2) was more effective than topical paromomycin [101]. PDT of 75 J/cm^2 red light performed 12 weeks also showed good results [102]. *Leishmania tropica* infection which proved to be resistant to various therapeutic regimes was effectively treated by PDT [103]. It is also more effective than topical paromomycin and methylbenzethonium chloride used for cutaneous Leishmaniasis [104].

PDT OF GASTRIC INFECTION

Peptic ulcer disease (PUD) is a common disease of human gastrointestinal tract, in which mucosal layer of GIT ulcerates. In most cases, PUD is associated with *Helicobacter pylori* infection. This endemic pathogenic bacterium is also linked to the development of gastric malignancies. In the first ever human trial, Wilder-Smith et al. [105] irradiated a zone of gastric tantrum in 13 HP-positive volunteers with blue light (410 nm, 50 J/cm^2) or endoscopic white light (10 J/cm^2) 45 minutes after oral ALA (20 mg/kg). HP number was greatly reduced in biopsies treated with ALA and blue or white light as compared to control. Hamblin et al. [106] showed that *H. pylori* naturally accumulates the photoactive porphyrins, coproporphyrin, and protoporphyrin, thus the bacterial cells should be intrinsically sensitive to photoinactivation without any added PS, especially when blue light is applied. Based on this hypothesis, Ganz et al. [107] successfully used endoscopically delivered blue light (405 nm, 40 J/cm^2) to eradicate *H. pylori* in regions of gastric antrum in 10 patients who were positive for the bacterium. Some patients had reductions in bacterial load approaching 99%. The same group also showed that whole stomach illumination with 405 nm light was safe as well as feasible [108] based on a pilot study in 18 patients with *H. pylori* infection. They obtained largest reduction in bacterial load in the antrum of the stomach (>97%) followed by body (>95%) and fundus (>86%) following endoscopic delivery of light with a diode laser coupled to balloon-encased diffusing fibers. The response was not dose dependent. However the eradication of bacteria was not sustained as urease breath test showed repopulation of bacteria in days following illumination.

CONCLUSIONS AND FUTURE PERSPECTIVE

The use of PDT to treat infections is in its infancy and faces several limitations that need to be overcome for its significant future application as therapeutics for infectious diseases. Key issues to address will be methods for delivery of both light and PS to sites of infection. Because delivery of light is almost by definition a localized process, PDT for infection is limited to the areas of body where light can be delivered relatively easily such as skin and body cavities. Thus antimicrobial PDT is more likely to be applied to exclusively localized disease as opposed to systemic infections such as bacteremia and sepsis. Furthermore there is need to determine accurate dosimetry, using appropriate illumination devices with well-defined parameters. PDT for infections will be likely be carried out by local delivery of the PS into the infected area by methods such as topical application, instillation, interstitial injection or aerosol administration into the airways. The effective selectivity of the PS for the microbes rather than the tissue is also an important concern to avoid an unacceptable degree of PDT damage to the host tissue in the area of infection. To be used in the clinical scenario, there are several factors of PS that need to be well defined. These include the physiochemical properties of the PS, dose to be delivered, rate of drug delivery, stability and ease of application and removal after use. Moreover the barrier properties of the target site and patient acceptability will also impact the antimicrobial PDT. Since PS are generally

deeply colored compounds, the possibility of unsightly dye remaining behind after PDT was used for infection must be considered. The ideal PS should be administered easily and safely, targeted appropriately, illuminated and activated at clinically useful wavelengths and pain free. There are several optimized PS molecules that have hundreds or thousands of time the potency than the ones used at present, but have not been subjected to toxicological and safety studies necessary for approval for human use.

Though successful methodology to treat infectious disease with PDT will be evolved in due course of time, it is important to realize that photoinactivation of microbes is an exclusively localized process and many other infectious diseases may continue to need systemic therapy unless PDT therapy is developed which can stimulate the host immune system. It is well established in that PDT in anti-cancer therapy induces host immune responses that have components of innate and adaptive immune systems. In principle the same process should operate when infections are treated with PDT. The effect of PDT on the host immune system is an important implication of PDT that is an open avenue that requires investigation in the area of infection. Another important aspect of antimicrobial PDT that needs to be studied is its ability to destroy secreted virulence factors. These are substances such as lipopolysaccharides and other proteins that that may be highly vulnerable to oxidation by the ROS generated during PDT. The ability of PDT to destroy secreted virulence factors has been shown for lipopolysaccharide and Pseudomonas proteases [109]. PDI of protease and other secreted virulence factors was thought to be responsible for better wound healing in *P. aeruginosa* infected wounds sterilized by PDT compared to those sterilized by silver nitrate [110]. The clinical applications of antimicrobial PDT have been slow but steady. Though limited clinical trials have been conducted for different diseases using PDT, its intensive use in periodontitis [111,112] has given hope that it can be likewise used to clinically treat a number of other infectious diseases.

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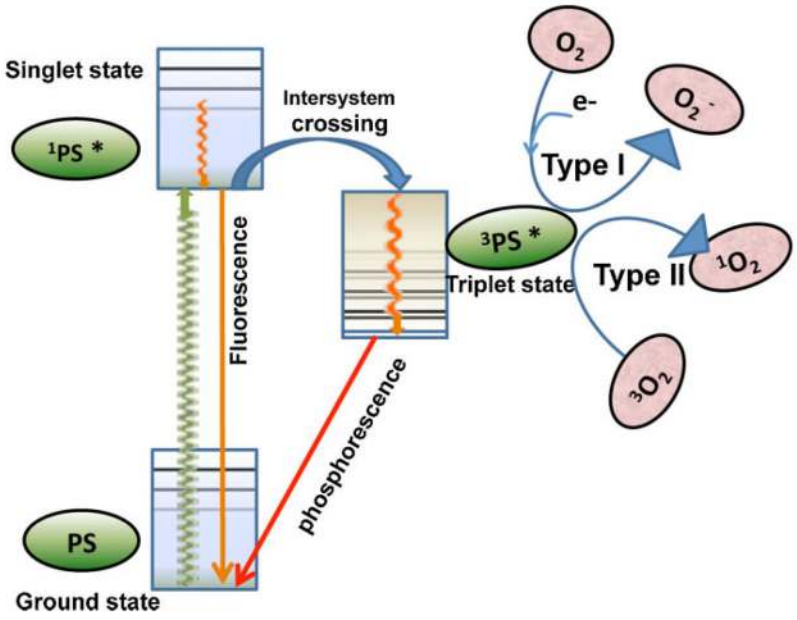

Fig. 1.

Photochemical mechanisms in PDT. Ground state photosensitizer molecule absorbs light that excites it to singlet state that can lose energy by fluorescence or can undergo intersystem crossing to long-lived PS triplet state that can carry out photochemistry or lose its energy by phosphorescence. Subsequently this photochemistry leads local production of reactive oxygen species such as singlet oxygen (Type II) or superoxide (Type I) that are cytotoxic to microbial cells and to host cells.

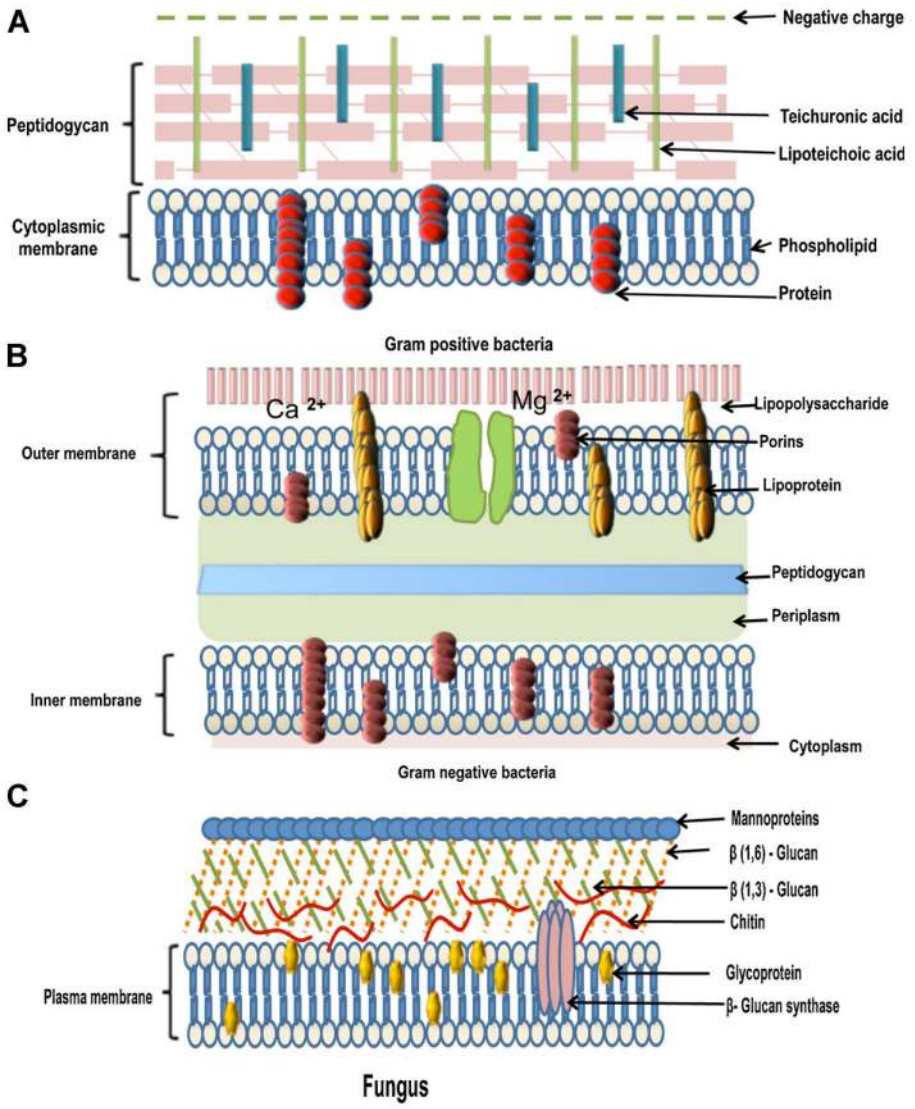

Fig. 2.

Cell wall structures of microbial pathogens. **A**: Gram-negative bacteria. **B**: Gram-positive bacteria. **C**: Fungal cells.

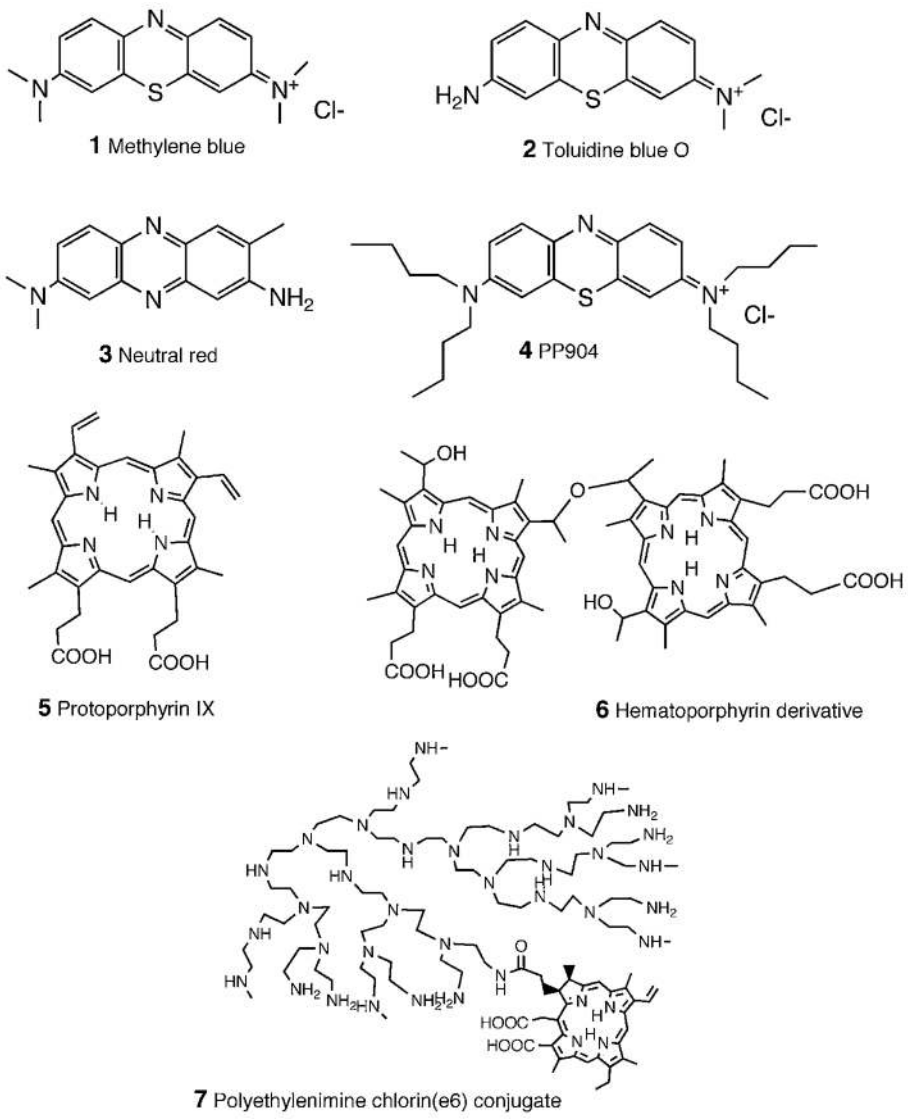

Fig. 3.

Chemical structures of photosensitizers that have been used in clinical applications of antimicrobial PDT. (1) Methylene blue, (2) toluidine blue O, (3) neutral red, (4) PP904 phenothiazinium dye, (5) Protoporphyrin IX formed from ALA, MAL or endogenously produced by bacteria, (6) hematoporphyrin derivative, (7) conjugate between polyethylenimine and chlorin(e6).

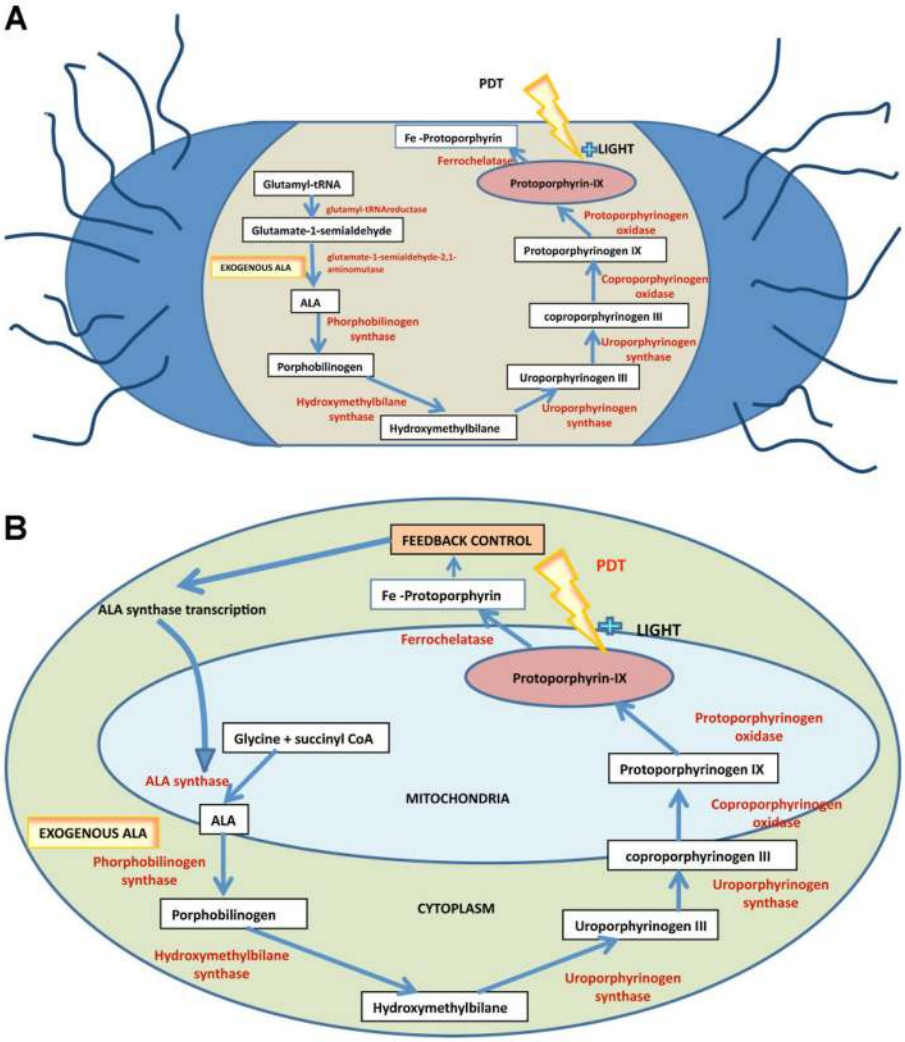

Fig. 4.

Heme biosynthetic pathways responsible for formation of PPIX from ALA. **A**: Porphyrin synthesis in Gram-negative bacteria. **B**: Porprhyrin synthesis is host mammalian cells.

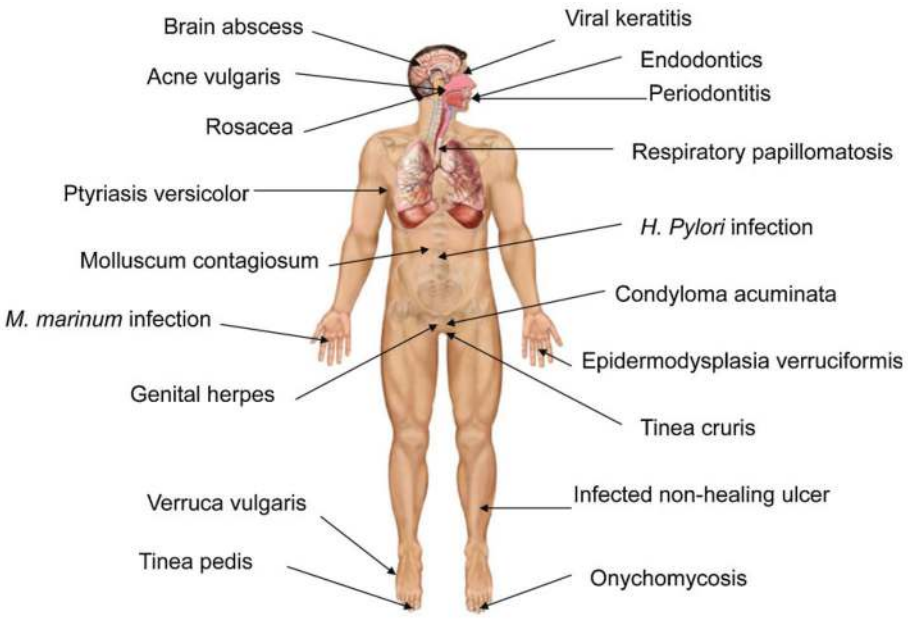

Fig. 5.
Schematic depiction of the range of human infections that have been clinically treated with PDT.

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TABLE 1

Infectious Diseases That Have Been Clinically Treated With PDT, the Causative Microorganisms and the Site of Infection

Disease	Causative agent	Site of infection	Photosensitizer used	Refs.
Localized infections	Bacteria	Brain abscess	Hematoporphyrin	[86]
		Nonhealing leg ulcers	Phenothiazinium dye PP904	[113]
			ALA	[88]
Herpes keratitis	Herpes simplex virus	Cornea	Proflavine	[22]
Genital herpes	Herpes simplex virus	Skin or mucous membrane of genitals	Methylene blue, neutral red	[23]
Recurrent respiratory papillomatosis	Human papilloma virus (HPV)	Respiratory tract (commonly in larynx)	Hematoporphyrin derivative—dihematoporphyrin ether	[25–27]
Epidermodysplasia verruciformis	HPV	Skin (particularly of hands and feet)	ALA	[28]
Verruca vulgaris (Warts)	HPV	Skin	ALA	[29–33]
Molluscum contagiosum	Molluscum contagiosum virus	Skin or mucous membrane	ALA	[34]
Condyloma accuminata	HPV	Genital/urethral warts	Polyhematoporphyrinether/ester	[37]
			Photolon	[38]
			ALA/MAL	[41–47,114,115]
Acne vulgaris	*Propionibacterium acnes*	Skin/sebaceous glands	Endogenous porphyrins	[49,53,116,117]
			ALA	[54–56,58–62,63,68]
			MAL	[66,67,65]
			Indocyanine green	[69]
			Chlorophyll	[70]
Rosacea	Undetermined but hypothesized to be connected to bacteria	Skin	MAL	[72]
			ALA	[73]
Erythrasma	*Corynebacterium minutissimum*	Skin	Endogenous porphyrins	[74]
Non-tuberculous mycobacterial ulcer	*Mycobacterium marinum*	Hands	Endogenous porphyrins	[75]
			ALA	
Malassezia folliculitis	*Malassezia furfur*	Skin	MAL	[84]
Ptyriasis versiccolor	*Malassezia* spp.	Axillae	ALA	[85]
Interdigital mycosis, tinea pedis	*Candida or Trichophyton*	Between toes	ALA	[77,78]
Tinea cruris	*Trichophyton* spp.	Groin	ALA	[79]

Disease	Causative agent	Site of infection	Photosensitizer used	Refs.
Onychomycosis	*Trichophyton* spp.	Toenails	ALA	[80–83]
Cutaneous Leishmaniasis	*Protozoa*	Skin	ALA	[101–104]
Periodontitis	*Bacteria (Porphyromonas gingivalis Fusobacterium nucleatum)*	Dental pockets and gingival tissue	Toluidine blue O	[89,91–93]
			Methylene blue	[94]
Necrotic pulp and periapical lesion, endodontics	*Bacteria (Enterococcus faecalis)*	Teeth/root canal	Toluidine blue	[98,100]
			PEI-ce6 conjugate	[98]
Peptic ulcer disease	*H. pylori*	Stomach	ALA	[105]
			Endogenous porphyrins	[107,108]