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Peer reviewed

**Review**

**The use of photodynamic therapy to treat hidradenitis suppurativa a review and critical analysis**

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**Abstract**

Hidradenitis Suppurativa (HS) is an inflammatory disease that results in abscesses, keloids, and fistulas. Acne inversa is likely to result from aberrant cellular immunity and dysfunction of the hair follicle in which coagulase negative staphylococcus (CONS) and perhaps other bacteria appear e.g. *Corynebacterium* sp. to play a role by creating biofilms and stimulating the immune system. One treatment that has been proposed for HS is photodynamic therapy. The cases series reported are small and not double blinded. As of October of 2104, 8 articles with 64 patients report success with photodynamic therapy using 5-aminolevulinic acid (PDT-ALA) or its methyl ester (PDT-MAL). One of these 8 reports noted superiority of the free methylene blue gel over niosomal methylene blue gel. Another report described success in a 27-patient trial using intralesional 5-aminolevulinic acid (ALA) in saline at a concentration of 1%. This was administered at a dose of 0.2 ml per cm<sup>3</sup> and an HS fistula was irradiated by a continuous 630-nm laser diode through a 1-mm thick optical fiber to 1 Watt per cm<sup>3</sup> for 3 minutes (180 Joules). However, 3 articles reported failure with PDT-ALA or pulse dye laser-mediated photodynamic therapy (PDL-PDT) and one article note 1 failure and 1 success. We suggest that it is the ability of PDT-ALA or PDT-MAL to break up the bio-film produced by CONS and other antibacterial effects that account for its success in treating HS in patients in whom bio-film plays a pivotal part of their pathogenesis. Other effects are also possible as well. Other mechanisms by which PDT may improve HS include cytotoxic effects, which cause selective cell necrosis, and immunomodulatory effects. The data suggests that if PDT is to be used, it should be with MAL or intralesional ALA.

Note that there are a variety of causes of HS. These include hyperkeratosis of in the follicular infundibulum, aberrant cellular immunity, down regulations of defensins in stage III HS, and the infiltration of neutrophils, mast cells, plasma cells, and lymphocytes into the affected follicle, among others. However, it is likely that in individual cases one cause is primary and others secondary. In conclusion, PDT is not a first line treatment for HS but in some cases could be added as an adjuvant to therapies such as clindamycin and rifampin.

**Introduction**

Hidradenitis Suppurativa (HS) is an inflammatory disease that results in abscesses, keloids, and fistulas. Acne inversa is likely caused or exacerbated by aberrant cellular immunity and dysfunction of the hair follicle in which coagulase negative staphylococcus (CONS) and perhaps other bacteria appear to play a role by stimulating the immune system [1,2,3,4]. In particular, other bacteria include: *Propionibacterium acnes* and *Propionibacterium granulosum*, [5] *Corynebacterium* species [6], *Streptococcus milleri* [6,7,8], and anaerobic *Streptococcus* or *Bacteroides* species [9] and perhaps gram negative bacteria e.g. *E*

*Coli*. These bacteria are more commensal instead of pathogenic as is *S aureus*. It is important to note that CONS are always found in deep tissue biopsies of HS [10, 11].

One treatment that has been proposed for treatment of HS is photodynamic therapy with photosensitizer. Some reports describe success in HS with photodynamic therapy with 5-aminolevulinic acid (PDT-ALA) or its methyl ester (PDT-MAL). Most clinicians recommend that MAL be used under occlusion for three hours before red light therapy. This article will review the data and suggest why PDT might work in some cases, but is not a treatment on par with the antibiotic treatment of clindamycin and rifampin or TNF- $\alpha$  blockers (TNFB) [1]. While considering photodynamic therapy we must recall that HS is more of a reaction pattern than a singular disease entity. Thus, there might be cases that could respond to PDT alone (mechanisms will be discussed herein). A few cases have been linked to genetic defects, but most are sporadic. HS can occur on any area of the body where there are follicles, but favors intertriginous skin, the axilla, the groin, and the perianal and perineal areas.

The skin manifestations of HS are varied and include pyogenic granulomas, acne inversa, abscesses, folliculitis, keloids, and fistulas. The severity of HS varies from patient to patient; each patient's immune system and genetic background make each case of HS different. The clinical heterogeneity of HS suggests that its response to treatment will be heterogeneous as well [4].

Most modern PDT applications involve three key components: a photosensitizer, a light source, and tissue oxygen. The combination of these three components leads to the chemical destruction of any tissues, which have selectively taken up the photosensitizer and have been locally exposed to light. The wavelength of the light source needs to be appropriate for exciting the photosensitizer to produce reactive oxygen species. These reactive oxygen species generated through PDT are free radicals (Type I PDT) generated through electron abstraction or transfer from a substrate molecule and a highly reactive state of oxygen known as singlet oxygen (Type II PDT). In understanding the mechanism of PDT it is important to distinguish it from other light-based and laser therapies such as laser wound healing and rejuvenation or intense pulsed light hair removal, which do not require a photosensitizer [12].

Photodynamic therapy (PDT) has been used for the treatment of a variety of conditions in inflammatory conditions in dermatology. PDT has been used to treat other cancers and non-malignant conditions such as acne vulgaris, granuloma annulare, localized scleroderma and lichen sclerosus, and photoaged skin. The substance that is activated by PDT is usually either 5-aminolevulinic acid (ALA) or its methyl ester (MAL), which is applied topically as a photosensitizer before activation with visible light. The advantages of topical PDT are the ability to treat multiple lesions simultaneously, low invasiveness, good tolerance, and positive cosmetic results [12]. The standard use of ALA-PDT in the United States today is for actinic keratoses. The typical treatment includes short-contact (about one hour) with ALA, full-face therapy, and one of the many light sources that is known to activate ALA, in particular blue light. Various modifications of the use of PDT have been made to adapt the procedure to HS.

PDT likely benefits HS because it disrupts the biofilm that is commonly created by *Staphylococcus epidermidis* and *Staphylococcus aureus*. The skin commensal and opportunistic pathogen *Staphylococcus epidermidis* is an important cause of nosocomial infections. However, although PDT might kill bacteria and disrupt biofilms, this might do nothing to change the course of the disease because CONS and other bacteria might rapidly re-colonize the area, again attracting the attention of the immune system [12].

Most papers have dealt with PDT for treatment of *Staphylococcus epidermidis* as an infection rather than as a mere colonizer. *Staphylococcus epidermidis* is a member of the normal skin flora. In the otherwise healthy patient, it is probably an occasional cause of minor skin infections. It may cause infections in wounds and especially around implanted surgical devices. Zeina et al [13] show that visible light with methylene blue was effective at killing *S. epidermidis*.

Gad et al [14] showed that the growth phase and extracellular of gram-positive pathogenic bacteria could be effected by PDT. Their data suggest that slime production and stationary phase can be obstacles against PDT for efficacy against gram-positive bacteria but that these obstacles can be overcome chemically by using cationic materials.

Sharma et al [15] investigated the effect of the photodynamic action of toluidine blue O (TBO) on the viability and structure of biofilms of *Staphylococcus epidermidis* and of a methicillin-resistant *Staphylococcus aureus* strain. Significant inactivation of bacteria was observed when staphylococcal biofilms were exposed to TBO and laser simultaneously. The effect was found to be light dose dependent. A confocal laser scanning microscopic study suggested damage to bacterial cell membranes in photodynamically treated biofilms. In addition, scanning electron microscopy provided direct evidence for the disruption of biofilm structure and a decrease in bacterial numbers in photodynamically treated biofilms. Furthermore, the treatment of biofilms with tetrasodium EDTA followed by PDT enhanced the photodynamic efficacy of TBO in *Staphylococcus epidermidis*, but not in *Staphylococcus aureus* biofilms. The results suggest that photodynamic treatment may be a useful approach for the inactivation of staphylococcal biofilms adhering to solid surfaces of medical implants. Tsai et al [16] found that photosensitizers entrapped in

micelles exert similar or better PDT efficacy than that of liposomes, which indicates these formulations may be useful for the treatment of local infections in the future.

Nisnevitch [17] examined the effect of three water-soluble photosensitizers: methylene blue, neutral red, and rose bengal on Gram-positive and Gram-negative bacteria. Nisnevitch compared the efficacy of these dyes, in their free form and encapsulated in liposomal formulations, against various bacterial strains and determined conditions for the effective use of encapsulated photosensitizers. Nisnevitch found that all three photosensitizers were able to eradicate the Gram-positive microbes *Staphylococcus aureus* and *Sarcina lutea*; methylene blue and rose bengal were effective against *Staphylococcus*. In the case of the Gram-negative species, methylene blue and rose bengal were cytotoxic against the *Shigella flexneri*; NR-inactivated *Escherichia coli* and *Salmonella* para B; rose bengal was effective in killing *Pseudomonas aeruginosa*. None of the examined photosensitizers showed activity against *Klebsiella pneumoniae*. Methylene blue and neutral red enclosed in liposomes gave a stronger antimicrobial effect than free photosensitizers for all tested prokaryotes, whereas encapsulation of rose bengal led to no increase in its activity. Nisnevitch suggested that encapsulation of photosensitizers can increase the photoinactivation of bacteria in some cases.

Sbarra [18] extended to *Staphylococcus epidermidis* strategies previously aimed at treatment of *Staphylococcus aureus* biofilms using photodynamic treatment (PDT) combined with chemotherapy or phagocytosis. A significant reduction in bacterial survival was observed when structurally distinct bio-films were exposed to the cationic porphyrin, tetra-substituted N-methyl-pyridyl-porphine (TMP) and simultaneously to visible light. Of note, the extent of biofilm clearance depended on its maturation stage; developing, young biofilms, were more sensitive to PDT than mature biofilms. Furthermore, PDT-treated biofilms exposed to vancomycin or subjected to phagocytic action of whole blood were almost completely eradicated. The data we obtained establish that PDT combined with antibiotics or host defenses may also be a useful approach for the inactivation of *Staphylococcus epidermidis* biofilms. The photodynamic effect of tetra-substituted N-methyl-pyridyl-porphine combined with the action of vancomycin or host defense mechanisms disrupts *Staphylococcus epidermidis* epidermidis biofilms. Figures 1 and 2 show patients who could possibly benefit from PDT.



**Figure 1.** Patient with hidradenitis suppurativa of the torso who might benefit from PDT. **Figure 2.** Patient with hidradenitis suppurativa of the axilla who might benefit from PDT

## Photodynamic therapy and efficacy for HS-Successes

Andino Navarrete et al [19] treated 5 patients with moderate to severe hidradenitis suppurativa with photodynamic therapy using ALA and a 635-nm light source. Treatment effectiveness was evaluated using the Sartorius severity score, the Dermatology Life Quality Index, and a visual analog scale for pain and disease activity. Significant improvements were observed with all 3 instruments and the effects remained visible at 8 weeks

Rodríguez-Prieto [20] treated 3 patients with intralesional PDT. The first patient was a nonsmoking 62-year-old man with a history of inflammatory bowel disease who developed HS lesions in both armpits during a 30-year period. The patient presented with multiple inflamed deep nodules and sinus tracts with occasional flares. He had been treated with oral corticosteroids and oral retinoids. After inflammation resolved, the fistulas healed. After 9 months of follow-up, there was no obvious clinical inflammation or recurrence of the fistulas. The second patient was a nonsmoking 43-year-old otherwise healthy man who presented with an 8-year history of HS in the axillary and groin regions. The patient had been treated with antibiotics, surgery, and

etanercept. The HS lesions again appeared on the lumbosacral area. The inflammation of the treated area resolved after 1 session of intralesional PDT (using the following protocol: 1% 5-aminolevulinic acid in saline solution formulated by the pharmacy department of our hospital was administered at an estimated dose of 0.1 to 0.2 mL/cm<sup>3</sup>). Occlusion was used to keep the solution in place for 3 hours. Afterward, the lesion was irradiated (intranodularly) with a diode laser beam of 630 nm applied with a fiber-optic probe at a strength of 1 watt (W) to each 1-cm<sup>3</sup> area for 3 minutes. Local anesthesia with bupivacaine at 0.5% to prolong the effect of the anesthesia and control postoperative pain was required. After 14 months of follow-up, no clinical recurrence was noted. The last patient was a 36-year-old man who had a nonsmoking 5-year history of chronic suppuration and pain secondary to HS in the right armpit. A physical examination showed an inflammatory nodule corresponding to the output of a fistula approximately 4 cm in diameter. He received treatments with oral and topical corticosteroids in addition to intermittent antibiotic treatment without success. Rodríguez-Prieto [20], performed intralesional PDT on the fistulous tract and inflammatory nodule; the patient had no pain or suppuration and complete resolution of symptoms after 7 months of follow-up.

Schwieger et al [21] treated 12 subjects with active HS with ALA PDT once weekly for four weeks. Nine subjects completed the study through the week 8 follow-up visit. Mean lesion counts were 11.25 at baseline, 6.5 at 4 weeks (50.8% reduction), and 7.5 at 8 weeks (29.9% reduction). Mean Global Severity Scores were 2.2 at baseline, 1.5 at 4 weeks, and 1.8 at 8 weeks. Mean DLQI scores were 17.3 at baseline, 13.1 at 4 weeks (27.2% improvement), 14.00 at 8 weeks (19.3% improvement) and 14.0 (19.3% improvement) at the final week (16-62 weeks). Three subjects (25%) had complete clearance and no active lesions 4 weeks after the final treatment. Treatments were more tolerable for subjects treated with blue light than with IPL.

Saraceno et al [22] report the case of a 29-year-old man affected by HS and pilonidal cysts since the age of 21. In the past, the patient was treated with antibiotics, corticosteroids, and retinoids, without significant clinical improvement. Treatment with MAL-PDT was started. A topical MAL cream (Metvix®) was applied to the affected areas with an occlusive dressing for 3 h and irradiated with a red light source. Therapy was repeated every 15 days for a total of nine applications. The patient completed a 6-month follow-up and achieved an almost complete clinical remission of the skin lesions (80%) and complete resolution of the itching and discomfort. This is the first case of HS associated with pilonidal cysts treated with MAL-PDT. MAL-PDT was effective and well tolerated in Saraceno's patient.

Gold in 2004 [23] reported 4 patients, not responding to standard HS therapy, who underwent short-contact ALA-PDT therapy utilizing a blue light for activation. One to two-week intervals between therapies was utilized for 3-4 total treatments and follow-up was for 3 months following the last treatment. All four of the patients tolerated the therapies well. Clinical improvements from 75-100% were noted in 11 of the patients. No adverse effects were seen during the treatments. The treatments were reported as being pain free and there was no downtime associated with these ALPDT treatments. Guglielmetti et al [24] reported a 41-year-old, otherwise healthy woman who presented with a 12-year history of extensive HS in the axillary and groin regions. Physical examination showed multiple nodules, abscesses, sinus tracts, granulation tissue, and scars. Histopathologically, a skin biopsy from the axilla showed neutrophilic suppurative folliculitis and a ruptured and inflamed follicular cyst compatible with HS. These lesions had been treated previously with antibiotics, corticosteroids, and retinoids, without significant clinical improvement. Two sessions of PDT-MAL 20% with Metvix® (PhotoCure ASA, Oslo, Norway) separated by an interval of 10 days were performed. The cream was applied topically to the affected areas and sealed with a cellophane wrap. Lesional skin was irradiated 3 hours later with a red light source (630 nm, Aktelite®, PhotoCure ASA) at a dose of 37 J/cm<sup>2</sup> for 8 min at a distance of 80 mm from the skin. Besides a moderate burning sensation and pain during illumination, no other side effect was noticed. She did not require treatment interruption. Erythema was observed immediately after illumination and remained for the next 2 days of the treatment. Guglielmetti et al [24] observed an impressive decrease in inflammation and exudate between 90% and 100% of the treated area after the second session. This effect was maintained at the 4-month follow-up evaluation (Figure 2). However, at the 12-month follow-up evaluation, she exhibited a mild relapse in some treated areas.

## **2014 Reports Endorsing PDT for treatment of HS**

Fadel [25] evaluated the efficacy and safety of methylene blue as a photosensitizer delivered as a niosomal gel for the treatment of HS using IPL and enrolled 11 patients with HS in a randomized split-body study. One side of each patient's body was treated with niosomal methylene blue gel and the other side was treated with free methylene blue gel. The affected sites were irradiated using IPL with a 630 nm filter. Patients were followed up at 1, 3, and 6 months after treatment. Drug release from the free methylene blue gel was significantly higher than from the niosomal methylene blue gel. Lesions showed 77.3% and 44.1% reduction on the niosomal methylene blue and unloaded (free) methylene blue gel sides, respectively. A significant reduction in the Hidradenitis Suppurativa Lesion, Area and Severity Index (HS-LASI) after treatment was elicited in both groups, with no pain, erythema, or hyperpigmentation.

Valladares-Narganes [26] subjected 27 patients diagnosed with HS and a longstanding presence of sinus tracts to intralesional PDT. Almost half (48%) were smokers. There was no washout period, but none of the patients received systemic therapy during

treatment or follow-up. The protocol involved individually evaluating all lesions with a modified Sartorius scale score. The evaluation was conducted using Doppler ultrasound to measure the length and depth of the sinus tracts and vascular structures that could be damaged. Intralesional 5-aminolevulinic acid (ALA) in saline at a concentration of 1% was administered at a dose of 0.2 ml per cm<sup>3</sup> of fistula. If the injury could be channeled, a catheter was used but was directly injected into different parts of the area. The inlet and outlet were covered to keep the solution within the fistula during the incubation period of 3 hours. Next, the lesion was intralesionally irradiated with the tip of the optical cable by a continuous 630-nm laser diode through a 1-mm thick optical fiber (LasAX630, INTERmedic, Spain) to 1 Watt per cm<sup>3</sup> for 3 minutes (180 Joules). The light was transmitted through a millimeter needle attached at the base by a device that allowed Valladares-Narganes to bring fiber to the tip. Local anesthesia was used, surrounding the surface treatment field and in both planes, superficial and deep, with 0.5% bupivacaine. Those patients who showed a suboptimal response or who had new lesions near the treatment site received another session. Before treatment, each region was scored with a modified Sartorius scale (i.e., 1 to 9 in each lesion). Patients were followed up at 1, 3, and 6 months. Valladares-Narganes[26] evaluated 27 HS patients at five anatomical locations: armpit (52%), inguinal-scrotal (26%), gluteal-sacral (11%), breast (7%), and popliteal region (4%). At 6 months follow-up, the degree of response was assessed. Most patients (21/27) had a good or complete response. The best results were obtained in single or isolated fistulas. In patients with multiple, interconnected, ill-defined and deep fistulas, second or third sessions were conducted with some degree of response and even complete response. In sum 10 (37%) complete responses, 11 (41%) good responses, and 5 (19%) partial responses were achieved. The axillae had the best results (6 of the 8 complete responses), including in patients with two arms involved. Only one patient experienced severe pain (score 9). Pain was moderate in 4 patients (VAS value 6 to 9) and the procedure could be completed. Adverse effects included postoperative pain, erythema and mild swelling. One patient complained of fever and an influenza-like illness that resolved itself. Serious adverse side effects, suppuration, or infections did not occur, which support an anti-infective role for PDT [26].

## Failure of PDT to ameliorate HS

Rivard and Ozog [27] reported two patients one male and one female with HS treated with PDT. They treated their female patient, with BLU-U Blue Light (DUSA Pharmaceuticals) PDT illuminator model 4170 blue light with ALA for 10 min initially. The dose was 6–10.9 J cm<sup>-2</sup> but the wavelength was not stated. Two weeks later a 60% glycolic acid peel was used, followed by two further PDT-ALA sessions with 12 min of blue light and a further peel. For the male patient, treatment was with the blue light initially for 18 min and 2 weeks later the Candela V-beam laser was used at 4–5 J cm<sup>-2</sup>, 6 ms pulse duration and a 10 mm spot size (no wavelength given). Rivard and Ozog reported that PDT was ineffective in the female patient they treated who also received glycolic acid peels. The male patient was said to improve but no indication of how this was determined is evident. No follow-up period for these patients was reported. Rivard and Ozog noted that in a series of 150 patients treated at Henry Ford Hospital, the FDA indication for the use of ALA-PDT in treatment of non-hyperkeratotic actinic keratoses of the face and scalp following a 14- to 18-hour drug incubation utilizing a blue light source for 16 minutes and 40 seconds but can also be used to treat basal cell carcinoma, acne and HS and other diseases[27].

Sotiriou et al [28] studied 5 HS patients with mean duration of disease of 3.2 years. Previous treatments included oral antibiotics, isotretinoin, and oral contraceptives. A preparation of ALA 20% (Medac GmBh, Hamburg, Germany) was applied topically and sealed with cellophane wrap. Lesions were irradiated 3 h later with red light (570–670 nm) from a noncoherent light source (Waldmann PDT 1200; Waldmann-Medizin-Technik, Villingen-Schwenningen, Germany) at a light dose of 20 J/cm<sup>2</sup> and a fluence rate of 50 mW/cm<sup>2</sup>. Patients received four treatments at 2-week intervals. All patients completed the four treatments, but none had a significant improvement. Poor penetration of the ALA may have been an important factor in the poor response.

Strauss [29] enrolled 4 patients with HS, three with axillary disease and one with groin disease. None of the four patients with HS treated with ALA-PDT had a significant improvement in the regional HS scores on follow-up and two patients showed deterioration. All four patients reported burning and stinging following each treatment, lasting for several days. [29] showed the absence of improvement after a maximum of three photodynamic treatments performed with 4-hour occlusion of ALA and the use of a red light. The PDL has a 595-nm wavelength well absorbed by protoporphyrin IX; it penetrates deeper in the skin than the blue light and allows a high amount of energy to be delivered in a shorter time. For some authors, it represents an interesting alternative to blue and red light for PDT and some successes have been reported in actinic keratosis or acne. Unfortunately, the results observed in these patients were disappointing. A partial response was observed after 1 month on the inflammatory lesions, but this could be linked more to the anti-inflammatory effects of the PDL rather than to the action of the PDT.

Passeron [31] et al treated four consecutive patients with HS with pulse dye laser-mediated photodynamic therapy (PDL-PDT). Despite systemic antibiotics, a combination of clindamycin 300 mg twice daily and rifampicin 300 mg twice daily for 10 weeks, followed with topical clindamycin for two patients and tetracycline 2 g/day in the two others, the symptoms were not controlled. Three of the four patients improved after 1 month of PDL-PDT, but after 3 months there was no difference between the treated and untreated areas. Because of the cost and intense pain observed with PDL-PDT, this modality cannot be advocated at this time.

# Conclusion

PDT shows mixed results for the treatment of HS. Its efficacy is based both on the ability of PDT to break up biofilms and to kill bacteria. It also might have effects related to cytotoxic effects, which cause selective cell necrosis, and immunomodulatory effects.

PDT activity can effect many bacteria besides CONS, and as the exact bacterial stimuli it is useful to have modality that is toxic for gram positive and negative and aerobic and anaerobic bacteria. This mirrors the utility of PDT for dissecting cellulitis [32, 33] i.e inconsistent but tantalizingly useful in a subset of cases. The different photodynamic agents, severity of disease, and small number of patients treated make comparisons between studies difficult. The optimal photosensitizing agent, ALA or MAL, has yet to be determined. The data suggests that PDT should be with MAL or intralesional ALA. It could be that intralesional injection of ALA or MAL is the best course, but large double-blinded studies are lacking. The work of Valladares-Narganes suggests that intralesional PDT using a laser diode attached to an optical cable is a promising new approach for the treatment of HS [26]. The consistency of effect of clindamycin and rifampin and TNF blocking agents make them the gold standards for formal treatment comparisons. It should be noted that clindamycin and rifampin and TNF blocking agents do fail to help some HS patients. Gold noted in [34, 35] that larger and more controlled clinical trials are warranted for the treatment of HS with ALA-PDT, yet such trials have yet to be performed. The inconsistent effect of PDT and need for further studies has been stressed by other authorities as well [36, 37, 38].

Even if PDT simply breaks up the biofilm of the bacteria that stimulates HS, it could be an adjuvant treatment. However, it can be painful, time consuming, and expensive; it may not be reimbursed by insurance. If the means of action of PDT is simply to break up biofilms and act as a cytotoxic antibacterial agent, the use of agents such as resorcinol 15% as a peeling agent may be preferred [39]. The enigmatic nature of HS continues to challenge clinicians. Efforts to incorporate PDT into the therapeutic armamentarium is to be lauded as physicians try and grapple with the challenge of treating HS in particular as it related to bacterial stimuli that can be abated with PDT.

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