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REVIEW ARTICLE

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Light-based treatment of pediatric port-wine birthmarks

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Abstract

Port-wine birthmarks (PWBs) are progressive vascular malformations with significant disfigurement and psychosocial morbidity; early light-based treatment has shown improved outcomes in the pediatric population. Somatic mosaic mutations underly the progressive nature of PWBs and explain the significant differences in response and heterogeneity of vessel architecture in the pediatric population when compared to the adult cohort. Here, we summarize a review of pediatric specific literature on the various light-based treatment modalities, including pulsed dye laser, near-infrared lasers, and intense pulsed light, providing the various indications, tips, advantages, and disadvantages for the pediatric dermatologist.

KEYWORDS

developmental defects, genetic diseases/mechanisms, laser, vascular malformation

1 | INTRODUCTION

Port-wine birthmarks (PWBs), often referred to as port-wine stains or capillary malformations, are progressive malformations composed of capillaries and post-capillary venules. They occur in up to 0.3% of newborns, present at birth as a pink to red patch, and often involve cosmetically sensitive areas including the face.[1] Over time, many PWBs darken in color, acquire secondary changes, including nodules and pyogenic granulomas, and develop soft-tissue hypertrophy that may involve underlying structures.[2,3]

PWBs are now known to be caused by somatic mosaic mutations in genes that control cell-cycle regulation, including *GNAQ*, *GNA11*, *PiK3CA*, and others that are also implicated in cell-cycle signaling.[4] This finding has transformed our fundamental understanding of their pathophysiology, as these genes share oncogenic pathways that result in synchronous, tightly regulated cellular proliferation and growth. PWB can be isolated, or syndrome-associated, including Sturge-Weber syndrome (SWS), phakomatosis pigmentovascularis (PPV), or *PiK3CA*-related overgrowth syndromes (PROS). Genotype-phenotype correlations exist for the most common mutations in vascular stains (*GNAQ*, *GNA11*, and *PiK3CA* hot spot, Figure 1).[4] While detailed mechanisms are not yet characterized, causative gain-of-function somatic mosaic mutations may explain the progressive development of nodularity, soft-tissue hypertrophy, and secondary vascular change of PWBs.[4-6]

Given the progressive disfigurement associated with PWBs, parents often seek early treatment with laser and other light-based modalities. Early treatment of PWBs reduces the likelihood and severity of disfigurement and psychosocial morbidity.[3,7] In particular, the development of vascular-selective lasers led to a therapeutic shift in the management of PWBs and remains the first-line standard of treatment. In this article, we review principles of light-based treatment for pediatric port-wine birthmarks.

1.1 | Selective photothermolysis

The use of lasers to treat vascular lesions relies on the theory of selective photothermolysis (SP); chromophores or light-absorbing targets can be targeted, heated, and damaged with minimal injury to the surrounding structures (Figure 2A).[8] For PWBs, the light-absorbing targets are oxyhemoglobin (absorption peaks at 418, 542, and 577 nm), deoxyhemoglobin (absorption peak between 750 and 800 nm), or methemoglobin (absorption at 620 nm, Figure 2B).[9]

Three elements are necessary to achieve desired clinical effects in PWB lesions. First, the wavelength chosen must be preferentially

absorbed by the target structure and reach sufficient depth. Second, the pulse duration must be less than or equal to the thermal relaxation time (TRT) of the target PWB vessels, which is, in seconds, approximately equal to the square of the vessel diameter. PWB vessel diameters range from approximately 10 to 300 μm in diameter. For PWB, this produces an optimal pulse duration ranging from 1 to 10 ms[10] Finally, sufficient fluence (energy per unit area) must be emitted to damage the target vessels, while minimizing collateral tissue damage. Vascular-selective laser wavelengths are absorbed by hemoglobin, converted to heat, resulting in photocoagulation, with injury and necrosis of the endothelial cells. Theoretically, these laser-tissue interactions lead to clearance of PWBs.

1.2 | Cooling modalities for light-based devices

Cooling modalities allow for the use of higher fluences to maximize thermal damage to the target chromophore while minimizing injury to normal skin, enhancing efficacy of light-based treatments by selectively cooling the epidermis.[11] The most common cooling strategies are contact cooling, cryogen spray, or forced air. Contact cooling and cryogen spray have the advantage of delivering cooling immediately before or after the light pulse, promoting rapid and spatially selective cooling without affecting the target chromophore temperature. Forced air is the least selective of the cooling methods. Forced air or prolonged contact cooling has the risk of decreasing temperature in superficial vessels thus diminishing efficacy. Post-treatment cooling with ice packs can be used for patient comfort. This does not reduce the risk of thermal damage during laser, and should not be used as a primary cooling modality.

2 | LASER AND LIGHT-BASED MODALITIES

The types of laser and other light-based modalities used in the treatment of pediatric PWB and efficacy results are discussed. Table 1 compares various modalities for pediatric PWB.

2.1 | Pediatric cutaneous anatomy and differences from adults

Significant heterogeneity in vessel architecture exists among PWBs and even within different regions of a single PWB, which may play a significant role in varied treatment responses. Many factors influence the efficacy of laser treatment of PWBs such as patient age, lesion size, color, localization, hypertrophy, and vessel architecture.[12-15]

Infant skin is approximately 40%-60% thinner than adult skin, with relatively less melanin and fewer hair follicles relative to adults.[16] These properties, along with other hypothesized mechanisms including elevated hemoglobin F in infants and smaller vessel size, make pulsed dye laser the treatment of choice in young children with PWB. It is the safest laser modality for treatment in the pediatric population.

2.2 | Preoperative considerations in the pediatric patient

Laser safety is paramount to protect from ocular damage. All present in the laser treatment room need appropriate eye protection specific to the laser wavelength. For patients undergoing facial treatments, wavelength-specific adhesive pads that cover the eyes or laser safe metal corneal shields, which are inserted under the eyelids, should be utilized.[17,18]

An assessment of an infant or child's ability to tolerate an in-office laser treatment with or without anesthesia (topical or general) is important for preoperative planning. Treatment with pulsed dye laser has been compared to the sensation of a rubber band snapped against the skin. For younger children, laser treatment may not be well tolerated and impractical without anesthesia, which provides both analgesia and immobility. While local anesthesia may be considered, it should be noted that topical anesthetics can result in blanching, and conversion of deoxyhemoglobin to methemoglobin, which may alter the chromophore target and make vascular lesions more difficult to view during treatment. However, the use of topical lidocaine 2.5% and prilocaine 2.5% (EMLA) cream has been effective as a topical anesthetic without adversely affecting efficacy of treatment.[19,20] General anesthesia (GA) results in vasodilation that can obscure the malformation. Prior to treatment, outlining the affected area with the use of a pen/pencil may be helpful, and our authors recommend the use of a white pen/pencil/eyeliner or yellow highlighter as black, blue or green will be absorbed by the 595 nm wavelength.

Infants treated early without GA may be given pacifiers dipped in sucrose syrup prior to treatment and during the procedure. A large Cochrane review meta-analysis found that this was effective in reducing procedure pain.[21] Sucrose mixed with sterile water works best if given two minutes before the procedure starts and can be repeated every 5 minutes during the procedure. Parents can often swaddle and cradle their child during the procedure. Additional staff may be needed to help stabilize the patient. Upon treatment completion, parents are recommended to comfort their child and encourage feeding. Most infants will often cease crying seconds to minutes after treatment completion. Ice can be used for comfort following the procedure in older children.

General anesthesia in children under the age of 3 is controversial, with the FDA emphasizing avoidance due to concerns for abnormal neurocognitive development.[22] Because studies have demonstrated improved clearance of PWB with earlier initiation of laser, physicians often treat in infancy without anesthesia.[18] While further studies are needed to determine the long-term psychologic effects of serial laser treatments in infants, families and clinicians should continue to participate in shared decision-making, weighing the risks of early treatment against the social stigma and

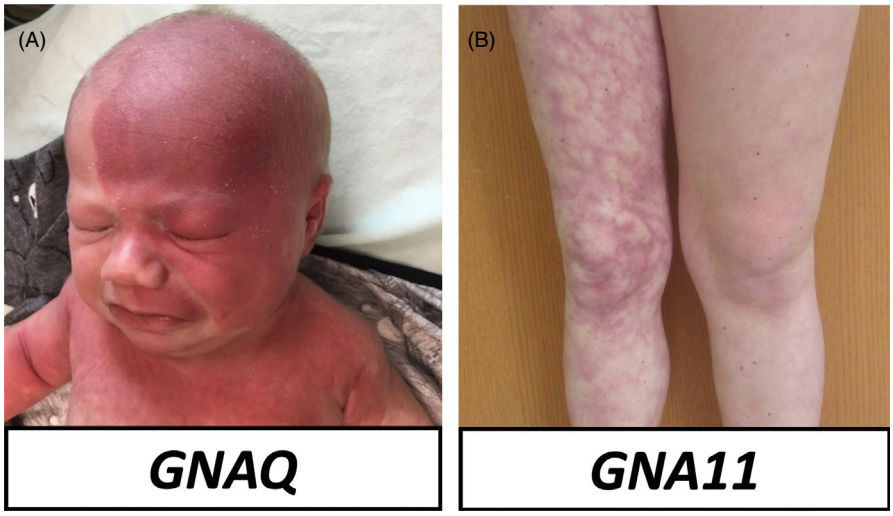

FIGURE 1 Genotype-phenotype correlation exists for the most common mutations in vascular malformations

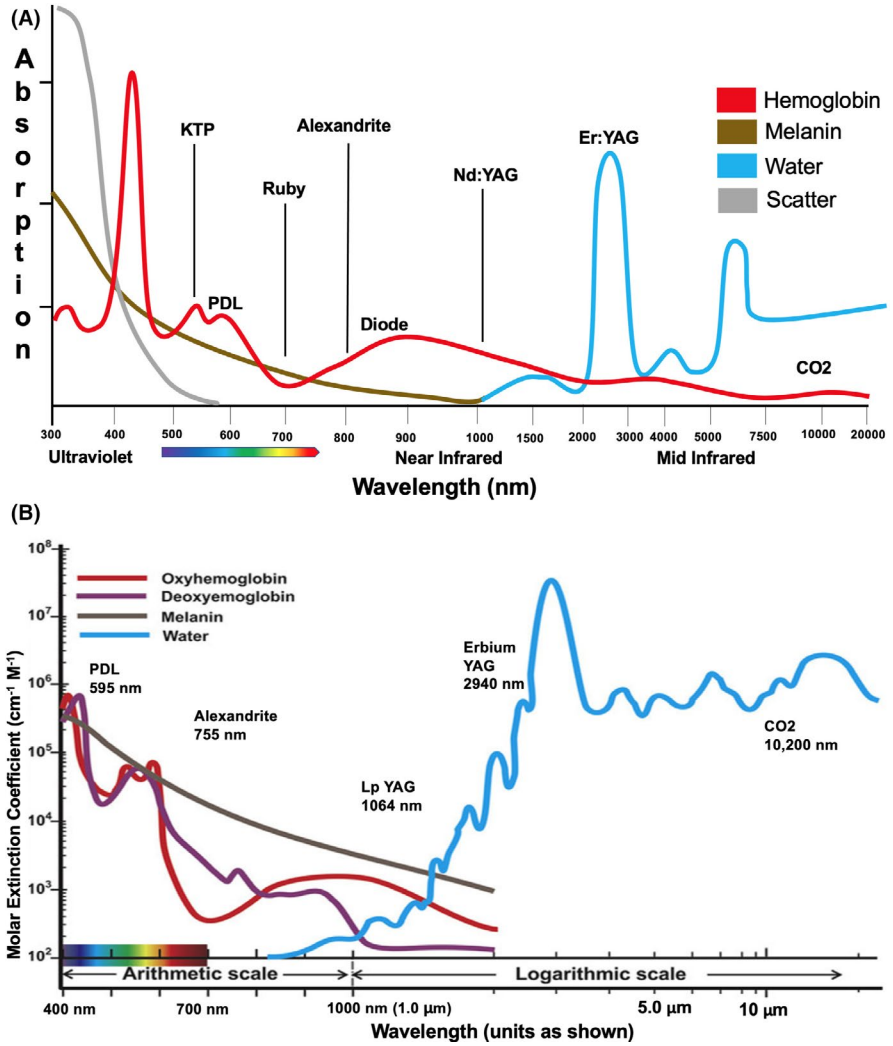

FIGURE 2 (A) Target chromophores in the spectrum of laser absorption. (B) Absorption spectrum of oxyhemoglobin, deoxyhemoglobin, melanin, and water. Longer wavelength lasers including Nd: YAG, which have a higher affinity for oxyhemoglobin relative to deoxyhemoglobin, have an increased risk for ulceration in vascular lesions

proliferative growth of PWBs over time. In this discussion, parents should be informed that numerous treatments (~8-10) are often needed for good clearance and that complete resolution may not be achieved.[13]

2.3 | Pulsed dye laser

The pulsed dye laser (PDL) was the first laser specifically developed for the treatment of vascular lesions and is the gold standard for

TABLE 1 Light-based therapeutic options for PWB in the pediatric population

Laser type (wavelength)	Indications	Advantages	Disadvantages
PDL (585-595 nm)	Gold standard for initial laser treatment Multiple studies show efficacy and tolerance, including in infants	Most published literature regarding safety and efficacy, supporting its use	Can only reach a depth of up to 1 mm Side effects include pigmentary changes (more common in darker skin phototypes due to interaction with melanin) and rarely scarring
LP Alexandrite (755 nm, near infrared)	Second-line for PWB Utilized in resistant, hypertrophic or nodular PWB	Penetrates deeper into the skin than PDL Preferential targeting of deoxyhemoglobin (DHB) may be advantageous for venous vessels Low epidermal melanin absorption	Scarring and pigmentation with high fluences
LP Nd:YAG (1064 nm)	Second-line for PWB Utilized in resistant or high blood flow PWB Typically used sequentially after PDL treatment	Highest depth of penetration for vascular-targeting lasers, reaching depths of 5-6 mm Lowest epidermal melanin absorption More effective for nodular hypertrophic PWB due to increased depth of penetration Faster purpura recovery time than PDL	Doses slightly above minimal purpuric dose can lead to irreversible scarring Narrow laser therapeutic window, requiring an experienced laser physician It is the opinion of the authors that this should not be used as treatment of PWB on the face of infants and school-aged children, as most patients will respond to PDL with appropriate parameters with reduced risk
IPL (390-1200 nm; modifiable with filters)	Second-line for PWB	Decreased post-treatment purpura Increased penetration relative to PDL	Side effects include pigmentary changes and scarring

PWB treatment in this country for its safety and efficacy. The 595-nm PDL with integrated epidermal cooling technology is what is commonly used in clinical practice. Given the heterogeneity of PWB and varying responses to laser treatment, there are no set guidelines on treatment parameters.

2.3.1 | Dosimetry

Laser tissue reactions result in end points that may be used as a guide for treatment. For PDL-treated PWBs, the therapeutic end point is usually purpura (Figure 3) limited to the laser spot size. Purpura is one end point, but does not guarantee complete vessel destruction, as regions of persistent perfusion can exist despite the presence of purpura. If the immediate purpuric end point is not achieved, the laser calibration could be checked, adjusted, and exposure-repeated. However, it should be noted that in cases where longer pulse durations are used, purpura may not be visualized. Increasing the fluence may not be the solution and adjustments of other features may be necessary, such as pulse width, wavelength, or evaluation of skin type.[23] Immediate skin shrinkage and metallic-gray blanching indicate nonspecific dermal injury and should prompt immediate reduction in treatment fluence or better skin cooling.[11]

2.3.2 | Efficacy

Given the proven safety and efficacy of PDL treatment in infants and young children, early treatment is recommended, with studies demonstrating 26%-32% complete clearance in infants <1 year of age, and 89%-100% of infants with greater than 50% clearance.[18,24] Pediatric PWBs have a better response to PDL treatment than adults with PWBs, often requiring fewer treatment sessions to achieve greater lightening, especially before the age of 1 year.[14,25] These results are attributed to smaller, more superficial vessels and thinner dermis in infants, enabling better accessibility of the vasculature to PDL and improved vessel destruction.[14,26] Among early-onset hypertrophic PWBs, complete clearance was rare (3%), but early treatment before the age of 2 resulted in higher response rates relative to later treatment (50% vs 24%; $P < .001$).[2] The general practice of our authors is to begin treatment as early as possible, optimally within the first few weeks of life. Regardless of age at initiation of treatment, the target chromophore (ie, hemoglobin) can be locally increased by utilizing several techniques, including increasing the ambient room temperature, application of heating pads or heated air from a hair dryer, brisk patting or rubbing, and improved patient positioning (eg, Trendelenburg for facial lesions).

Treatment intervals used in infants vary in the literature, and our authors treat every 4-6 weeks. Other clinicians found on retrospective review that with shorter intervals (2-, 3-, 4-week), efficacy results were equal or greater to 6- to 12-week intervals with no difference in complication rates in skin types I-III.[24] In contrast, a recent prospective study of East Asian infants found that frequent PDL treatments (2-week intervals) did not necessarily increase efficacy and resulted in more side effects such as eczematous dermatitis.[27] This may be attributed to the increased melanin in East Asian skin. Thus, longer treatment intervals may be considered for darker skin types and determination can be made based on treatment results. Treatment can

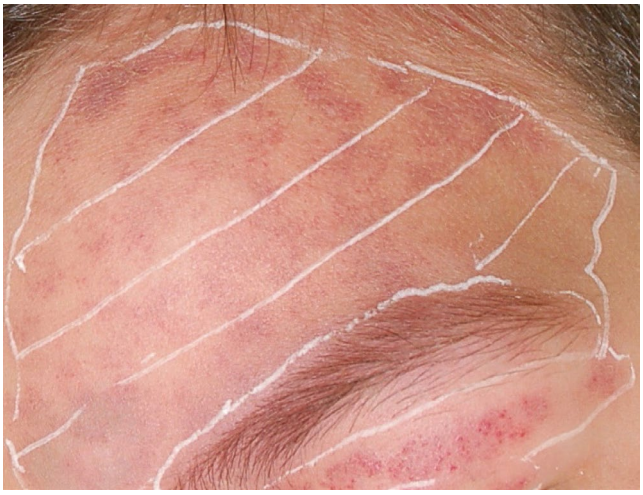

FIGURE 3 Purpura immediately following treatment with pulse dye laser of a PWB that was delineated preoperatively with white marker

be continued until near or complete resolution or until lesions are unresponsive to further treatment.

2.4 | Postoperative care

To reduce swelling post-treatment, ice packs can be used with application for 10-15 minutes each hour for four hours. A bland moisturizer, such as petrolatum, should be applied to the treated areas if blisters develop. In addition, photoprotection with sun avoidance and broad-spectrum SPF 50 sunscreen is recommended to reduce the effects of epidermal damage. The use of topical steroids may be considered to reduce acute adverse effects from treatment.[28]

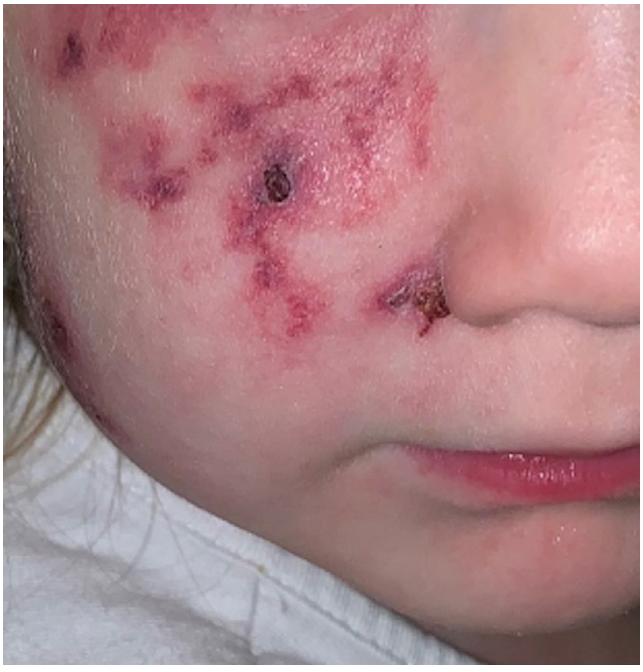

FIGURE 4 Small area of crusting following pulse dye laser treatment of a PWB. This resolved after a few days of emollient and did not lead to any scarring

2.5 | Side effects and potential complications

Expected consequences of PDL laser treatment for PWBs include purpura and edema. Purpura typically fades over 1-3 weeks, while edema is transient. Blistering and crusting occurs when there is epidermal injury (Figure 4), and most commonly results from overlapping or stacked pulses, use of high fluence or improper cooling.[23] Crusted or blistered areas should be treated gently with petroleum jelly and moist bandaging until healed. Pigmentary changes can occur from damage to melanosomes or due to post-inflammatory changes, but often resolve over time. Rarely cutaneous depressions have been reported with PDL; this sometimes resolves without intervention.[29]

3 | PDL-RESISTANT PWBS

Savas et al summarized the factors that contribute to PDL-resistant PWBs. These include age, size of lesion (>40 cm^2), anatomic location (peripheral limbs and centrally located lesions, ie, medial cheeks, upper lip, and nose), dermatomal distribution (V2 lesions), skin thickness (hypertrophic or nodular PWB), vessel depth (>400 μm), and vessel diameter (<40 μm).[13] In addition, many PWB lesions extend 3 to 5 mm deep, with depth of penetration of PDL at 585 to 600 nm limited to approximately 1 mm.[15] Deeper dermal capillaries from PWB are most likely inaccessible to PDL; those that escape complete photocoagulation will continue to proliferate and grow due to the genetic mutations underlying the birthmark.[13,15] Because of the differences between pediatric and adult cutaneous anatomy, these features are less likely to be seen in the pediatric population. Redarkening can also be seen in PWBs over time and is hypothesized to occur due to their progressive genetic etiology, lack of complete eradication of vessels, and suboptimal laser parameters.[30]

3.1 | Near-infrared lasers (long-pulsed (LP) Alexandrite, 755 nm, and LP Nd:YAG, 1064 nm) for resistant PWB

The longer wavelength lasers, the long-pulsed 1064 nm Nd:YAG and long-pulsed 755 nm Alexandrite, penetrate 50%-75% deeper into skin than PDL, with less optical scatter and epidermal melanin absorption. For this reason, they are typically used for PDL-resistant PWB including those with nodular or hypertrophic change, and patients with the darkest skin phototypes due to decreased wavelength interaction with melanin. However, treatment should be reserved for laser surgeons with significant experience, as scarring can occur at or just above purpuric doses. Due to their lower hemoglobin absorption, they require higher fluences for sufficient vessel

photocoagulation. Corneal damage has been reported with the LP Nd:YAG laser, even with metal corneal shields in place, and it should not be used near the periorbital region.[31] In addition, the LP Nd:YAG laser has a higher absorption for water, leading to nonselective bulk tissue heating that can result in significant scarring (Figure 5).[32]

3.1.1 | Dosimetry

With more deeply penetrating wavelengths of the near-infrared (IR) lasers, the appropriate therapeutic end point is different than PDL, and this recognition is critical to minimize the risk of epidermal damage. These lasers enable deeper penetration than PDL, but should be delivered at or barely above the lowest fluence that causes purpura. The immediate end point of both the Alexandrite and the Nd:YAG is an immediate transient gray-blue that evolves over minutes to hours into a deep purple and a purple-blue color, respectively. In addition, the purpura threshold fluence for these lasers can vary widely between patients compared to PDL and should be determined individually through test spots. Overtreatment can result in a dermal burn, which is evidenced by a persistent gunmetal gray color, and invariably leads to scarring.[32,33]

3.1.2 | Efficacy

The majority of studies with the near-IR lasers are in adults, most of whom have developed hypertrophy or recalcitrant PWB, with fewer cases of resistant pediatric PWBs. Even with the use of near-IR lasers in conjunction with PDL, complete PWB clearance is rare. In a small case series of resistant PWBs treated with Alexandrite laser, only mild to moderate responses were achieved in pediatric patients, with no cases of complete clearance. Moreover, several cases were complicated by blistering, pigmentary changes, and isolated scarring.[34] The LP Nd:YAG (1064 nm) laser is typically used in the same refractory patient population, or for those with darker skin types (V-VI), as the 1064 wavelength has a lower relative affinity for melanin, with decreased risk for post-inflammatory change. However, the LP Nd:YAG laser has a higher relative affinity for oxyhemoglobin than deoxyhemoglobin (in contrast to the Alexandrite), and this leads to a significantly higher risk for ulceration and scarring. In spite of this, most patients with refractory PWB fail to clear with the LP Nd:YAG laser. A study of PDL-resistant or hypertrophic PWBs treated with LP Nd:YAG demonstrated that 35% (7/20) of patients experienced moderate to significant improvement (>61% clearance), with no cases of complete clearance. Side effects in this small study were significant and included pigmentary changes (25%; 5/20) and scarring (15%; 3/20).[35] For laser-naive patients with PWBs, the use of the LP Nd:YAG (1064 nm) laser in children and adults with skin types III-IV found that only 19% (25/130) of patients had >75% clearance, and efficacy correlated with older age (>20 years), location on the neck, and purple-colored lesions. Cases with the poorest efficacy were in infants 6-9 months old with smooth, flat, pink lesions.[36]

In summary, the use of near-IR lasers should be considered only for PDL-refractory or nodular/hypertrophic PWBs, and should be used with caution due to increased potential for adverse events including scarring. Potential side effects are similar to PDL with potential for epidermal or dermal injury, resulting in blistering and metallic-gray blanching, respectively. In general, we recommend against the use of near-IR lasers in infants and young children since this population is more likely to respond to PDL repeated at regular intervals, with appropriate parameters.

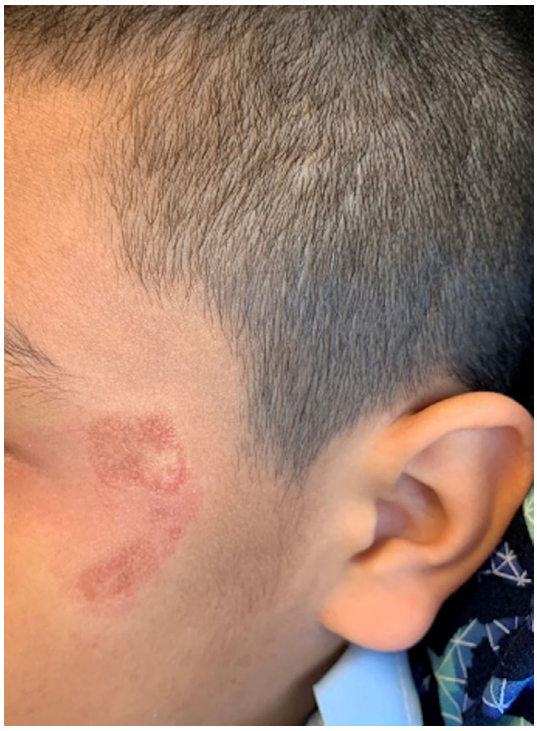

FIGURE 5 Scarring from use of LP Nd:YAG laser on the face of a child with a PWB

3.2 | Intense pulsed light

Intense pulsed light (IPL) may be used and considered for PDL-resistant patients or when PDL is unavailable given that is has less adverse effects than the near-IR lasers and enables deeper penetration than PDL. A retrospective study found 70%-100% clearance rate in 75% (21/28) of previously untreated and 58% (7/12) of previously treated PWB. Among the previously treated lesions, resistant purple lesions had greater treatment efficacy, which may be explained by the increased depth of penetration by IPL.[37] In a small study of resistant PWBs, only 46.7% (7/15) of patients were responders, but the majority of IPL responders had 75%-100% clearance with more favorable side effects when compared to PDL. All non-responders had lesions on the medial cheek.[38] These studies suggest that IPL may have benefit in a subset of patients with resistant PWB.

IPL should not, however, be considered for initial therapy in children with conventional PWB prior to failure of PDL with appropriate parameters (30% vs 65% clearance with PDL).[39] Moreover, lesions in children showed poorer clinical results than adults (64.7% vs 86.8%).[40] Adverse effects include pigmentary changes (6%-11%), transient crusting (3%-20%), and superficial blisters (8%).[37,41]

3.3 | Photodynamic therapy

Photodynamic therapy (PDT) represents an alternative two-step treatment option for PWB that results in free-radical damage to endothelial cells. PDT has site specificity with damage limited only to photoilluminated areas after exposure to a photosensitizer.[42] While there are no large, randomized control trials on the safety and efficacy of PDT in children, hematoporphyrin monomethyl ether photodynamic therapy (HMME-PDT) for the treatment of pediatric PWB has been reported to be safe with higher excellent responses in PDT than PDL (25%-29% vs 10%), but similar overall response rates (90.2% vs 89.1%).[43,44] The HMME photosensitizer is given intravenously. Purple lesions and lesions located on the forehead, cheek, and jaw showed better responses to PDT than PDL. However, the Zhang study had suboptimal PDL parameters (585 nm, 4.8-6.5 J/cm^2 without dynamic cooling), which may result in underestimations of PDL efficacy rates.[43] The combined treatment of PDT and PDL in PWBs of the extremities shows promise for an efficacious and safe treatment modality with improved results over PDT or PDL alone.[45]

Common side effects of PDT treatment include burning and pain during treatment. After treatment, edema, purpura, crusting, and pigmentary changes may be seen. Generalized photosensitivity is a significant side effect which occurs in all patients, requiring photoprotection and sun avoidance days to weeks after treatment, depending on the half-life of the photosensitizer used.[43] In addition, to control pain and motion during PDT, general anesthesia is often needed in the pediatric population. The complexities of costs and clinical utility of this methodology (injection of photosensitizer, light avoidance, general anesthesia, longer procedure time) should be weighed against other vascular laser modalities.[43,44]

4 | FUTURE DIRECTIONS

In summary, while lasers have brought significant improvement for pediatric patients compared to other treatment modalities, current laser therapy remains inadequate in complete clearance for most PWBs. The somatic mosaic genetic underpinnings of PWB explain the invariable resistance of PWB to laser, as residual mutated cells that escape complete destruction will invariably continue to proliferate and grow. Deep vessels may be inaccessible to the device wavelength, extra-large vessels may not be amenable to complete photocoagulation, and a mismatch of parameters to vessel size and depth may compound the poor response.

Discovery of the shared molecular basis between vascular anomalies and cancer has set the stage for repurposing targeted therapies originally developed for malignancy, unlocking the potential for pharmacologic blockade of activated pathways. Optimizing treatment will require a precision-based, multimodal approach with better imaging techniques to individualize parameters, improvements in laser technology, and targeted molecular therapy to prevent progression and recurrence.

CONFLICT OF INTEREST

Kristen M Kelly, MD: drug donated by Allergan; equipment provided to clinic by Solta, Syneron/Candela, Thermi RF; Vivosight, R2 Derm; consultant for Shanghai Fudan-Zhangjiang Bio-Pharmaceutical Co., Ltd, Syneron-Candela, Allergan, Sciton; research supported by Allergan, ASLMS; NIH; Sturge-Weber Foundation, UC Irvine ICTS. Beth A Drolet, MD : consultant and medical advisory board member for Venthera. LIsa M Arkin, MD: research equipment from Candela. Research funding from Sturge Weber Foundation, Pediatric Dermatology Research Alliance and the Dermatology Foundation. The remaining authors have no conflict of interest.

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