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Consensus Statement for the Management and Treatment of Port-Wine Birthmarks in Sturge-Weber syndrome

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Abstract

Importance: Sturge-Weber syndrome (SWS) is a sporadic, neurocutaneous syndrome involving the skin, brain, and eyes. Consensus recommendations for management and treatment are limited or do not exist. This statement focuses on recommendations for addressing the major cutaneous manifestation of SWS, the port-wine birthmark (PWB). The treatment recommendations are currently applicable to all patients with a PWB.

Objective: This consensus statement aims to consolidate the current literature with expert opinion to make recommendations that will guide treatment and referral for patients with PWB.

Evidence Review: Twelve national peer-recognized experts in dermatology with experience treating SWS patients were assembled. Key topics and questions were formulated for each group and included: (a) risk stratification; (b) optimum treatment strategies; and (c) recommendations regarding light-based therapies. A systematic PubMed search was performed of English language articles published in 2008-2018, as well as recent studies identified by the expert panel. Clinical practice guidelines were recommended.

Findings: Treatment of PWB is indicated to minimize psychosocial impact and diminish nodularity, and potentially tissue hypertrophy. Better outcomes may be attained if treatments are started at an earlier age. In the United States, pulsed dye laser (PDL) is the gold standard for all PWB regardless of the lesion size, location, or color. When performed by experienced physicians, laser treatment can be performed safely on patients of all ages. The choice of using general anesthesia in young patients is a complex decision which must be considered on a case by case basis.

Conclusions and Relevance: These recommendations will help guide clinical practice and decision making for SWS patients and patients with isolated PWB, and may improve patient outcomes.

Introduction

There is a critical need for a consensus statement regarding an approach to managing Sturge-Weber syndrome (SWS). In 2018, The Sturge-Weber Foundation (SWF) published a comprehensive review of research needs regarding the pathogenesis, clinical features, and treatment options of SWS[1]. Our consensus aims to provide clinical practice guidelines to guide the care of the major dermatologic feature of SWS, the port-wine birthmark (PWB).

SWS is a sporadic, congenital, neurocutaneous syndrome involving the skin, brain, and eyes with an estimated prevalence of 1 in 20,000 to 1 in 50,000 live births. It is caused by a somatic mosaic mutation in the *GNAQ* gene located on chromosome 9q21, affecting neural crest cells emanating from the forebrain region, and resulting in vascular abnormalities of the cutaneous forehead, cerebral cortex, and eye[2,3]. SWS patients typically have at least 2 of the following 3 components: facial PWB, vascular malformation in the brain, and vascular

malformation in the eye. However, clinical manifestations vary and work-up and treatment is guided by the extent of these manifestations.

The goals of this consensus are to 1) review the literature and provide an approach to risk stratification and evaluation of PWB; 2) offer guidance on diagnostic workup for patients with suspected or newly diagnosed SWS; and 3) assess current treatment options for PWB in light of age and condition severity. The treatment recommendations are currently applicable to all patients with a PWB.

Methods

Twelve national experts in dermatology were consulted to develop a consensus statement on the management and treatment of cutaneous manifestations of SWS, as part of a larger consensus statement. The panel was created from a list of experts provided by the SWF, who had significant experience in treating SWS patients and patients with PWBs and who agreed to participate. Three key needs were identified: (1) risk stratification and evaluation of PWB (2) optimum treatment strategies for PWB; and (3) specific recommendations regarding light-based therapies. The expert group was divided into 4 subgroups who formulated questions to address each topic. An extensive literature review was performed using PubMed for English-language papers published between 2008 and 2018, an arbitrarily selected date range to explore articles within the past 10 years. Articles before 2008 or after 2018 were added by the expert panel based on importance. Search terms included “Sturge-Weber syndrome” plus the following: “clinical presentation”, “pathogenesis”, “risk prediction”, “port-wine birthmark or port-wine stain”, “diagnostic workup”, “triage”, “management”, “treatment”, “laser therapy”, “light-based therapy or treatment”, “photodynamic therapy”, “infantile hemangioma”, and “nevus simplex.” 112 manuscripts were identified; 76 were relevant to dermatology. These were narrowed to 41 articles based on abstract or full text review, and supplemented with ten additional references identified by the expert panel. Publications were assigned to questions for each key topic and distributed to each subgroup, who were asked to develop responses and key guidelines, which were consolidated into 10 key points (Table 1). The first author drafted the manuscript and presented to all 4 subgroups for electronic discussion and modification. The drafts were circulated to the full expert panel and edited multiple times until each individual gave final approval.

Dermatology

Risk Stratification and Evaluation of the Port Wine Birthmark—Key Point 1: The characteristic skin manifestation of Sturge-Weber syndrome (SWS) is a port-wine birthmark (PWB), a congenital vascular malformation composed of malformed capillary-like vessels, which is present at birth as a typically unilateral, bilateral, or centrally located, well-demarcated, pink to red patch on the face.

The best predictor for SWS is a facial PWB involving any part of the forehead, and including the upper eyelid and the midline frontonasal prominence[2] (Fig 1a). The distribution appears to follow the patterns of embryological vasculature, challenging the long-held belief of a “trigeminal nerve” etiology. It is important to note that not all patients with PWBs will develop SWS; however, certain distributions indicate an increased risk.

Previous studies demonstrated a 7%-28% SWS risk in patients with a PWB in what was previously described as a V1 distribution[4]. More recent studies have demonstrated that hemifacial, forehead, and median PWB locations are associated with increased SWS risk[5](Fig 1b). Bilateral PWB or those that extend from the forehead to include the cheek and skin overlying the mandibles have a higher risk of SWS[6,7], but the forehead location is the strongest independent predictor of SWS risk[2,8]. PWB in SWS most often involve the lateral forehead, and are less commonly localized to the midline forehead, but there are exceptions, as even a small PWB of the midline forehead can be associated with severe neurologic disease[7].

Facial PWB persist throughout life and may become darker red or red-purple in color over time. Particularly when located over the mid-face, facial PWB may develop progressive vascular ectasia/thickening, soft tissue hypertrophy, and proliferative nodules which are prone to bleeding and discomfort, and less commonly infection[9]. On histologic examination, most such nodules represent vascular ectasias, pyogenic granulomas or arteriovenous malformations[10], although other epithelial and mesenchymal hamartomas have been described[11]. Progression may result from both vascular ectasia and specific genetic alterations with PWB that lead to soft tissue hypertrophy[12]. Progressive changes are uncommon before puberty. Eczematous skin changes (e.g. “Meyerson phenomenon”) have been observed within PWB earlier in childhood, particularly in children with pre-existing atopic dermatitis[13].

Key point 2: The best timing of evaluation of a facial PWB is at birth.

Identification of an at-risk facial PWB, especially those involving the forehead, should prompt an eye examination for congenital glaucoma and neurology referral. In cases in which the diagnosis is uncertain, referral to an experienced specialist is appropriate. Differential diagnoses include segmental infantile hemangioma that may warrant PHACE workup, or other capillary malformations such as nevus simplex. Early diagnosis of a PWB affords the option of maximizing early laser treatments, which may be performed without the need for general anesthesia and may improve treatment outcome[2].

Determination of the Optimum Treatment—Key Point 3: There are a number of factors that should be considered regarding treatment, including minimizing psychosocial impact, diminishing nodularity and potentially tissue hypertrophy, and financial considerations for the family.

Patients and parents seek treatment for several reasons, including lesion appearance that affects quality of life, confidence, and self-esteem, among other psychosocial issues[14]. Laser treatments may prevent or treat the proliferative nodules that can develop over time[15]. There is no clear evidence that laser treatment definitively prevents tissue hypertrophy. However, superficial overgrowth may be minimized if adequate vessel removal is achieved. Because laser light is unable to reach deep vessels, PWB may still develop hypertrophy despite treatment.

Key Point 4: In the United States, light-based devices are the standard of care for PWB treatments, and pulsed dye laser (PDL) is considered first-line.

Pulsed dye laser (PDL) has the longest history of efficacy and safety for treatment of PWB and many studies support this device as the gold standard[4,16]. For infants, PDL is considered standard of care in the United States. Experienced surgeons can safely perform laser surgery in patients of all ages.

Several other wavelength lasers (532 nm, 755 nm, 1064 nm) and intense pulsed light (IPL) have been used for PWB treatment. These can be used for all PWB, but are especially useful for those that have demonstrated PDL resistance. The longer wavelengths (755 nm, 1064 nm) may help target larger or deeper vessels, such as patients with nodular and hypertrophic lesions[4,17]. These devices also target hemoglobin but have a higher risk of damage to non-targeted tissue than PDL. There are few or no randomized controlled trials with these alternative devices and children have not been included in the vast majority of reports. However, small studies have shown promising results for recalcitrant PWB[18,19]. The Alexandrite laser is the most commonly used alternative when PDL is inadequate[20]. Long-pulsed Neodymium-doped yttrium aluminum garnet (Nd:YAG) may also be considered, but has a particularly narrow margin of safety[4].

A variety of fractionated ablative devices designed for facial rejuvenation have also been used for PWB treatment. Many of these devices use infrared laser pulses (CO2, Erbium:YAG, and Erbium:Glass), while others use bipolar radiofrequency ablation to coagulate skin and blood vessels. In small studies, combined with PDL, efficacy has been demonstrated with these devices for recalcitrant PWB[21,22].

When discussing the option of laser treatment with families, the following should be addressed:

1) Pain control: Topical anesthetics, epidermal cooling methods, injection of local anesthetics, nerve blocks, intramuscular pain medication such as meperidine, or general anesthesia can minimize discomfort[15]. Multiple factors are involved in choosing the optimal method of pain control for a patient, including but not limited to: patient age and state of health, PWB location and extent, availability of methods dependent on practice, surgeon experience, and parent/child preference.

2) Adverse effects: [See Key Point 10]

3) Financial obligations. Costs may include professional fees of the laser surgeon, anesthesia fees, facility fees, etc.

4) Clinical outcomes. Realistic expectations should be set with families as complete PWB clearance is rarely achieved[23]. PDL can achieve 50%-90% clearance and the majority of patients will have more than 50% lightening[4]. Most patients require eight to ten treatments or more for optimal results; however, touch-up treatments are frequently needed even after an initial successful series of lightening. Despite considering factors listed below, response is difficult to predict.

Several factors have an effect on treatment response. Patients with lighter skin types have a better treatment response.[24] PWB on the face and neck respond better than those on the extremities[16]. PWB on the lateral face respond better than those in the central face[21,25]. Proximal extremity lesions respond better than distal extremity lesions[16]. The eyelids and neck are at higher risk for blistering and scarring and this should be considered when selecting laser parameters. Based on the authors' experiences, individuals with PWB associated with SWS may be more resistant to laser. Pink, red, and reticular lesions respond better than those that are purple and geographic shaped[16,24]. Not unexpectedly, PWB with overgrowth will show a lesser response than those that are flat, smooth, and not associated with contour change[4,16].

5) Psychosocial consequences. It is imperative that short- and long-term well-being of the patient from a psychosocial perspective is considered and, above all else, the patient's safety.

Key Point 5: Light based devices are still first line treatment for PWB in patients with skin of color, however higher rates of side effects may be seen than in lighter-skinned patients, mainly dyspigmentation and atrophic scarring. Moderate energy densities, less pulse overlap, and increased cooling are recommended in the treatment of patients with darker skin types to minimize risks.

PWB occur in patients with all skin types and this is probably the greatest factor influencing treatment. While limited clinical studies exist for certain races/ethnicities, specifically East Asian and Indian patients, and in certain skin types, particularly Fitzpatrick skin types V and VI, a few studies provide insight for pigmented skin. In one study, PDL was used successfully in Indian patients without permanent side effects, although the lightening achieved was modest in nature[26]. This study included 74 flat, non-hypertrophic and 24 hypertrophic PWB with a mean of 7.3 and 8.5 treatment sessions, respectively. The mean lightening achieved was 54% in non-hypertrophic and 40% in hypertrophic lesions[26]. In East Asian populations, PDL has also been used safely and successfully. While the percentage of improvement varies, reported results are slightly better than the aforementioned Indian study with fewer treatment sessions. In 239 Korean patients, 51.9% showed a good to excellent response, defined as >51% percentage clearance, after a mean of 4.29 sessions[27]. In another study of 848 Chinese patients, a 69.9% response was achieved after a mean of 6.2 sessions. Notably, this study also underscored the importance of patient age in treatment response, with a 93.9% response rate reported in children treated during the first year of life and only a 25% response rate in treated adults over age 50 years.[28].

Importantly, while patients of darker skin types can experience improvement in their PWB, they are also at higher risk of persistent dyspigmentation, atrophy, and scarring[16,20]. In general, moderate fluences, less pulse overlap, and increased cooling are recommended in treating patients with skin of color, and patients should be counseled that transient hyperpigmentation is common[26].

Key Point 6: There are a number of alternative therapies that have been investigated for PWB that do not respond to traditional laser and light-based treatments.

Alternatives to laser or IPL therapy can be divided into four groups: 1) adjuvant medications 2) photodynamic therapy; 3) surgery; 4) corrective cover-up.

1) Adjuvant medications: There are currently no adjunctive medical therapies that have demonstrated consistent impressive efficacy for PWB[29,30]. Several small studies have reported some benefit for PDL + topical imiquimod versus PDL alone[29]. Similarly, a few small studies and case reports demonstrated some benefit of topical rapamycin as an adjunct with PDL[31,32], but no consistent benefit over PDL alone.

2) Photodynamic therapy (PDT): PDT involves the intravenous administration of a photosensitizer (various forms of porphyrin) followed by exposure to a light source, producing intravascular singlet oxygen molecules that destroy local tissue. Although PDT is not currently performed in the U.S., studies from China have shown promising results[33-35]. Approximately 20% of patients experience hyperpigmentation and scarring. Notably however, melanin does not influence the efficacy of PDT, so this treatment can be performed in patients of all skin types, although patients with darker skin types will still be more susceptible to pigmentary change post-treatment[4,16].

3) Surgery: Surgery can be used to selectively debulk thick PWB or lip hypertrophy, remove larger nodules, or completely remove small lesions in which the resulting surgical scar is acceptable to the patient.

4) Corrective cover-up: A variety of cover-up products and concealers are available for dermatologic conditions and can be utilized in PWB patients.

Laser and Light-Based Therapies—Key Point 7: The interval between laser treatments is dependent on a multitude of factors. No optimal interval has been established by scientific evaluation, thus treatment interval must be tailored to each patient.

The interval between laser sessions depends on age, skin type, PWB location, pain tolerance and presence of hypertrophy, nodules or blebs. It is also influenced by resolution of prior purpura and/or hyperpigmentation, convenience, financial limitations and potential restriction of activities after treatments. Only a few, small studies in infants have analyzed the interval between PDL treatment sessions ranging from 2 weeks to 3 months[36,37]. These studies do not provide a clear recommendation on shorter vs longer interval times, although a subset of patients appear to benefit from shorter time intervals. Importantly, these studies demonstrate the safety of PDL when performed at short intervals.

In older children, adolescents and adults, it is uncertain if there is an optimal timing interval between treatments. A small pilot study in adults suggested that 2-week treatment intervals resulted in greater lightening compared to 6-week intervals[38]. Other studies have failed to show this benefit[39]. While shown to be safe, shorter treatment intervals may result in a higher incidence of undesirable effects, especially in patients with darker skin who often benefit from longer intervals to avoid post inflammatory hyperpigmentation. It is also important to allow purpura to heal before treating again as the increased chromophore can increase the risk of adverse effects.

Key point 8: Greater rates of lightening, and possible prevention of future darkening and hypertrophy may be attained if treatments are started at an earlier age. The main goal of treatment is to ensure healthy and adequate psychosocial development and minimize the stigma associated with PWB.

Based on expert observations and limited studies, treatment of PWB at an earlier age, particularly in the first year of life, results in better outcomes. Factors associated with improved prognosis in young children include proportionately smaller PWB, more superficial and smaller blood vessels and less melanin as a competing chromophore for PDL. Liu et al. found greater efficacy when treatments were started before age six years[40]. Other studies have found better responses in infants younger than one year of age, particularly with smaller PWB less than 20 cm^2 [41-43]. However, these studies are limited by their retrospective nature and relatively short follow-up periods. Larger case-control studies are needed to support this observation.

Current laser technology is less successful in reverting progressive PWB changes of darkening, hypertrophy and nodularity. Thus, performing laser treatment in early childhood may prevent or minimize these changes. Limited, retrospective studies support the concept that early treatment inhibits progression, however, longitudinal studies are needed[44,45]. It has been shown that patients 7-16 years old with facial differences, including PWB, experience impaired health-related quality of life[46]. The negative impact on the psychosocial development and quality of life is one of the main reasons to pursue early treatment. This impact on psychosocial development may be diminished when lightening of the PWB is attained at an earlier age.

Key Point 9: PDL in young patients is a safe treatment option with low incidence of permanent complications when operated by an experienced laser surgeon.

The risks associated with laser treatment of PWB can be categorized in two groups: risks inherent to the procedure itself and risks associated with the method of analgesia. The latter will be discussed with the next key point. The risks associated with PDL are focused upon here because it is the most widely used and safest treatment option in infants and toddlers, particularly when compared to longer wavelength vascular lasers. The safety and tolerance of PDL was also greatly improved with the addition of cooling technology. Immediate treatment effects include erythema and purpura, which has traditionally been considered the desired clinical end-point. The risk of complications have been reported to be less than 10% and are most often temporary[40]. Swelling may occur, which in most patients is mild, except in the periorbital or lip area. Dyspigmentation may occur in response to direct epidermal and melanocyte damage, and is most common in patients with darker skin types, tanned skin, and recent sun exposure. Sun protection is advised before and after treatments. Temporary blistering may occur. Erosions, ulcerations and secondary infection are rare when appropriate laser settings are used and adequate post-procedure skin care is followed. Permanent scarring, both atrophic and hypertrophic, is one of the most feared potential complications of PDL but has an estimated incidence of below 1%[40,47,48]. Lastly, PDL treatment over hair-bearing areas may cause hair loss, which is typically temporary, but can be permanent in an estimated 1.5%-2.6% of cases[49].

The most serious potential complication resulting directly from PDL is ocular damage, especially when treating the periorbital area. Appropriate use of corneo-scleral eye shields is mandatory when treating the skin within the orbital rim. Laser-specific eye shields may be used when treating outside the orbital rim. Special care must be taken when PDL is performed without sedation as young patients may move in response to the discomfort. Securing the patient's position and ensuring eye protection is crucial when treating infants and toddlers. Parent(s), nursing staff and the laser surgeon must also wear adequate protective eyewear.

Key Point 10: Laser treatments can be associated with significant discomfort. The choice of using general anesthesia is complex and informed, shared decision making with the patients and their parents/guardians must be employed.

A critical factor to consider when treating younger patients is the pain and discomfort associated with laser treatments. While treatment of small and moderate size lesions is fast and generally well tolerated, patients with larger PWB may experience significant discomfort in which case topical anesthesia or sedation may be considered. Topical anesthetics including lidocaine preparations, can be used safely but there is a risk of methemoglobinemia, especially in infants[15]. Published guidelines regarding topical anesthesia should be followed if this option is chosen[50].

General anesthesia requires careful consideration given the potential risks and higher cost. General anesthesia carries a risk of cardiorespiratory complications, which is highest in the neonatal period and decreases with age[51,52]. It is common practice to wait until at least 6 months of age to use general anesthesia for elective procedures, but procedures prior to this age can be performed without general anesthesia. Anesthesia should be administered by providers specialized in pediatric care to reduce the risk of perioperative morbidity. The risk of neurotoxicity with potential long-term negative effects on neurological development has gained recent attention. The FDA advises caution in patients younger than 3 years requiring repeated use of general anesthesia and sedation during surgeries or procedures, which is relevant to the management of PWB as multiple treatments early in life are often performed. The FDA warning was based predominantly on pre-clinical data, and ongoing trials will help to further clarify this risk[53]. Until more information is available, the decision to use general anesthesia or sedation must be carefully considered.

When general anesthesia or sedation is not used, young infants have an advantage over toddlers. PDL treatment without general anesthesia is more safely and efficiently performed in infants, since the area of involvement is proportionally smaller and the patient's position and eye protection can be secured more easily[54]. Nevertheless, the potential impact of painful procedures must be carefully weighed. Noxious stimuli early in life may lead to short-term and possibly long-term effects in behavior, particularly towards medical care[55]. Parental stress and satisfaction must also be considered when making this decision.

Conclusion

This consensus statement provides expert consensus on identification and risk stratification, optimal treatment strategies, and recommendations for light-based therapies for patients with PWBs.

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Key Points

Question:

What are clinical practice guidelines for treatment and management of port-wine birthmarks (PWB), including those associated with Sturge-Weber syndrome?

Findings:

In this consensus statement, 10 key recommendations were formulated.

Meaning:

These recommendations will help guide clinical decision making for these patients.

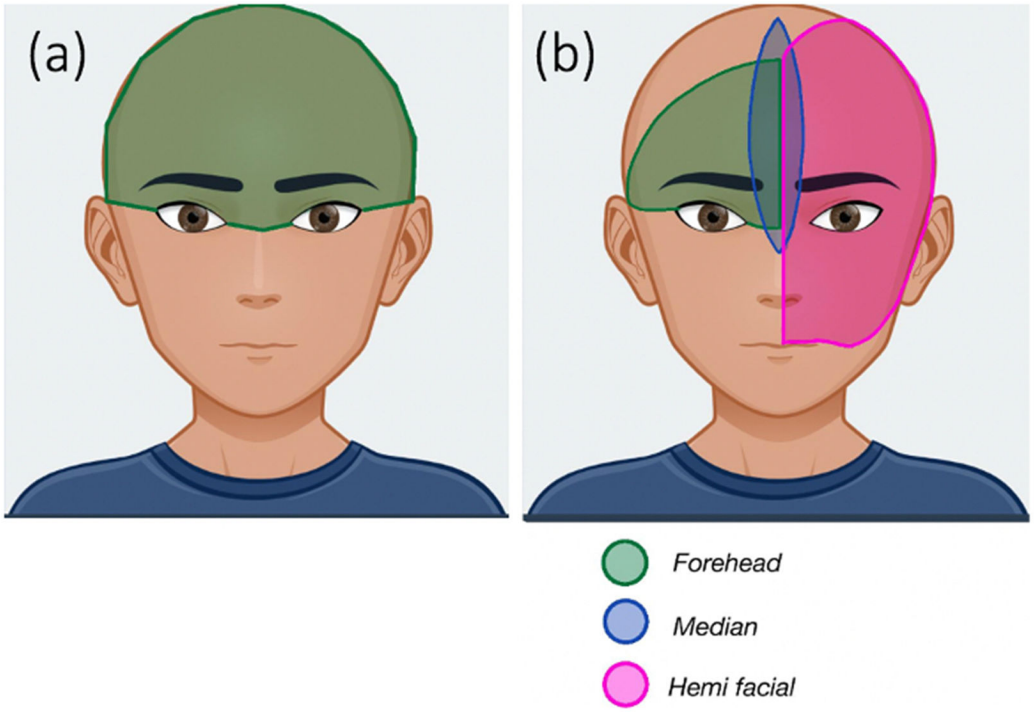

Fig 1.
(a) and (b) Port-wine birthmarks with the highest risk of Sturge-Weber syndrome

Table 1.

Key Points for Dermatological Management and Treatment in SWS

1. The characteristic skin manifestation of Sturge-Weber syndrome (SWS) is a port-wine birthmark (PWB), a congenital vascular malformation composed of malformed capillary-like vessels, which is present at birth as a typically unilateral, bilateral, or centrally located well-demarcated, pink to red patch on the face.
2. The best timing of evaluation of a facial PWB is at birth.
3. There are a number of factors that should be considered regarding treatment, including minimizing psychosocial impact, diminishing nodularity and potentially tissue hypertrophy, and financial considerations for the family.
4. In the United States, light-based devices are the standard of care for PWB treatments, and pulsed dye laser (PDL) is considered first line.
5. Light based devices are still first line treatment for PWB in patients with skin of color, however higher rates of side effects may be seen than in lighter-skinned patients, mainly dyspigmentation and atrophic scarring. Moderate energy densities, less pulse overlap, and increased cooling are recommended in the treatment of patients with darker skin types to minimize risks.
6. There are a number of alternative therapies that have been investigated for PWB that do not respond to traditional laser and light-based treatments.
7. The interval between laser treatments is dependent on a multitude of factors. No optimal interval has been established by scientific evaluation, thus treatment interval must be tailored to each patient.
8. Greater rates of lightening, and possible prevention of future darkening and hypertrophy may be attained if treatments are started at an earlier age. The main goal of treatment is to ensure a healthy and adequate psychosocial development and minimize the stigma associated with PWB.
9. PDL in young patients is a safe treatment option with low incidence of permanent complications when operated by an experienced laser surgeon.
10. Laser treatments can be associated with significant discomfort. The choice of using general anesthesia is complex and informed, shared decision making with the patients and their parents/guardians must be employed.