Title
Infantile hemangiomas: our current understanding and treatment options

Permalink
https://escholarship.org/uc/item/5jt8q9km

Journal

Authors
Soliman, Yssra S
Khachemoune, Amor

Publication Date
2018

DOI

Copyright Information

Peer reviewed

Infantile hemangiomas: our current understanding and treatment options

Yssra S Soliman[1] BA, Amor Khachemoune[2,3] MD

Affiliations: [1]Albert Einstein College of Medicine, Bronx, New York, USA, [2]State University of New York Downstate, Department of Dermatology, Brooklyn, New York, USA [3]Veterans Health Administration, Department of Dermatology, Brooklyn, New York, USA

Corresponding Author: Amor Khachemoune MD, FAAD, FACMS, Veterans Affairs Hospital & SUNY Downstate, Dermatology Service, 800 Poly Place, Brooklyn, NY 11209, Tel: 718-630-3725, Fax: 718-630-2881, Email: amorkh@gmail.com

Abstract

Infantile hemangioma (IH) is the most common vascular tumor of infancy, affecting up to 10% of all infants. Our understanding of IH and its management has greatly evolved. The etiology of IH is unclear but hypoxia is thought to play a key role. Furthermore, GLUT1, IGF2, and HIF-1-α are thought to be important mediators. Current management options include active observation, medical treatment, and surgical intervention. The goals of treatment are preventing cosmetic disfiguration, psychosocial distress, and life-threatening complications. Infantile hemangioma should be managed with an individual, patient-centered approach. Generally, uncomplicated IH can be observed up to 18 months. However, IH should be treated in the setting of bleeding, ulceration, functional compromise, or eventual failure to regress.

Keywords: infantile hemangioma, ISSVA, GLUT1, angiogenesis, propranolol

Abbreviations are listed in Table 1.

Introduction

Infantile hemangioma (IH) is the most common vascular tumor of infancy. It is believed to occur in up to 10% of infants [1]. It is a benign, clinically heterogeneous vascular tumor [2]. Infantile hemangioma often appears by the second week of life [3]. However, deeper hemangiomas may not be apparent to the eye until the 2nd to 4th month of life. Infantile hemangiomas commonly appear on the head and neck but may appear anywhere on the skin or in visceral organs. Classically, the hemangiomas display rapid growth during the third month of life, followed by slow involution [4]. By 48 months, approximately 90% of cases will have regressed [5].

This article aims to review the epidemiology, clinical presentation, genetics, histopathology, associated syndromes, evolution without treatment, and treatment options of infantile hemangioma. The primary database used was PubMed. We searched the following terms: 'infantile hemangioma,' 'strawberry hemangioma,' and 'segmental hemangioma.' These terms were combined with the following: 'diagnosis,' 'genetics,' 'treatment,' and more specific terms including 'GLUT1' and 'HIF-1-α.'

Historical note and evolving classification

Infantile hemangioma has been reported in the literature under a variety of names including strawberry nevus, capillary hemangioma, juvenile

Table 1. *Abbreviations.*

GLUT1	Glucose Transporter 1
IGF-2	Insulin-like growth factor 2
HIF-1-α	Hypoxia-inducible factor 1-alpha
IH	Infantile hemangioma
IH-MAG	Infantile hemangioma – minimal arrested growth
ISSVA	International Society for the Study of Vascular Anomalies
EPC	Endothelial Progenitor Cells
KMP	Kasabach-Merrit Phenomenon
PG	Pyogenic granulomas
PDL	Pulsed Dye Laser
RICH	Rapidly involuting congenital hemangioma
NICH	Non-involution congenital hemangioma

hemangioma, and strawberry mark [6]. The term "strawberry naevus" was used to describe IH in 1894 by Patterson [7, 8]. However, it was Lister who first set out to characterize them in a more specific manner. The lesions were common in infants but not in adolescents or adults. He differentiated the growths based on depth into bright-red superficial lesions, blue-tinged deep lesions, and mixed lesions with central, superficial vasculature surrounded by a deeper base.

Eighty-eight years later, Mulliken and Glowacki set to differentiate IH from vascular malformations [9]. They noted that the variety of nomenclature led to confusion among clinicians. For example, capillary hemangioma was used interchangeably to refer to both IH and non-regressive port-wine stains. Vascular tumors including IH differ from vascular malformations based on pathophysiology. Simply, IH are believed to be the product of increased angiogenesis leading to proliferation of endothelial components [9]. Vascular malformations, including port wine stains, are believed to be related to impaired innervation leading to poor, tortuous vessel tone [10].

Mulliken and Glowacki differentiated IH based on two distinct histological phases [9]. The rapid, proliferating phase was defined by increased endothelial hyperplasia. The slower, involuting phase was defined by fibrosis and fatty deposition. In 1997, their findings were adopted by the International Society for the Study of Vascular Anomalies (ISSVA) and the nomenclature standardized [11]. The ISSVA classification was recently updated in 2014 [12]. Today, IH is considered a benign vascular tumor and classified based on pattern, depth, association with other lesions, and identified using immunohistochemical markers (Table 2).

Pattern is described as focal, multifocal, segmental, or indeterminate pattern. Types of IH are defined by depth such as superficial, deep, mixed, or reticular/abortive/minimal growth. It is interesting to note that "reticular morphology" was first proposed in 2007 [13]. Previous nomenclature included "hemangioma with port-wine stain-like appearance," infantile hemangioma with minimal

abortive growth, and even livedoid infantile hemangioma [14-17]. Bessis et al. proposed using reticular infantile hemangioma with minimal arrested growth (RIH-MAG) to emphasize the reticular morphology when discussing infantile hemangiomas that display minimal proliferation. RIH-MAG is significant in the literature owing to possible association with lipoatrophy [14].

Epidemiology
The incidence of IH is believed to be between 4-10% [18, 19]. It is difficult to determine the exact incidence because of differing nomenclature [18]. Furthermore, IH does not appear immediately at birth, leading to misdiagnosis and under diagnosis.

Several risk factors have been identified for IH including female sex and Caucasian race [18, 19]. Females have between a 3:1 to 5:1 increased risk of IH [18]. There is debate in the literature about whether family history is a true risk factor for IH. Some authors associate family history with a recall bias [19]. Others have identified potential genes inherited on chromosome 5q [20]. It is unclear whether infants of mothers who underwent transcervical chorionic villus sampling have a higher risk of IH [21, 22].

Etiology
The etiology of IH is still being studied. However, several theories have been proposed. It has been speculated that hypoxia plays a key role [23]. Studies have shown that prematurity, multiple gestations,

Table 2. *Infantile Hemangioma Classifications.*

Morphology
Focal
Multifocal
Segmental
Indeterminate
Depth
Superficial
Deep
Mixed
Reticular/abortive/minimal growth
Immunohistochemical Markers
GLUT1
IGF-2

advanced maternal age, and, especially, low birth weight less than 1500 grams are risk factors for IH. Placental insufficiency is a known cause of low birth weight. It is believed that an increase in angiogenic factors, such as HIF-1-α, in response to hypoxia in utero leads to compensating, proliferating hemangiomas [23, 24].

Histology and markers
The histological characteristics of IH can be divided into that of the proliferative versus involuting phase [9]. The proliferative phase is characterized by increased endothelial cell activity and formation of syncytial masses lacking distinct vascular architecture, especially decreased capillary lumina. Then, laminated basement membranes are seen under endothelium. In the involuting phase, cellularity decreases while fatty deposits and fibrous tissue become evident. Hemangiomas that do not completely regress show endothelial proliferation intermingled with fibro-fatty infiltration.

One study aimed to understand whether mediators of endothelial progenitor cells (EPC) are increased during the proliferative phase of IH [24]. Specimens were obtained from patients with proliferating hemangiomas. Hypoxia induced factors, essential to post-natal angiogenesis, were measured. VEGF-A and MMP-9 were measured in the blood and SDF-1-α, MMP-9, VEGF-A, and HIF-1-α were measured in tissue sections. All factors were indeed increased in children with proliferating hemangiomas. Furthermore, it was found that estrogen acted synergistically with hypoxia in vitro to increase EPCs found in hemangiomas.

An important marker of IH is Glucose Transporter 1 (GLUT1). This marker aids in differentiating IH from other vascular entities such as vascular malformation, hemangioendothelioma, or pyogenic granuloma [25]. This marker is present despite the proliferative activity of the IH lesion [26]. GLUT1 is a high affinity glucose transporter and sensor of hypoxia [25, 27]. North et al. demonstrated that GLUT1 is also expressed in placental chorionic villi, suggesting a placental origin for IH [28]. Another marker is insulin-like growth factor 2 (IGF-2), which is expressed, in high amounts during the proliferative phase and in lower amounts during involution [29].

IGF-2 has been shown to increase levels of GLUT1 expression. Further investigation is needed to understand the exact roles of GLUT1 and IGF-2 in the pathogenesis of IH.

Emerging genetics
Most IH occurs sporadically. However, Walter et al. attempted to delineate genetic factors by studying several families with seemingly autosomal dominant inheritance of IH [20]. They identified a possible linkage to 5q31-33. This region corresponds to the following genes thought to contribute to angiogenesis: fibroblast growth factor receptor-4 (FGFR4), platelet-derived growth factor receptor-beta (PDGRFB), and FMS-related tyrosine kinase-4 (FLT4).

In one study, one-third of infants with large segmental hemangiomas of the head and neck were found to have posterior fossa malformations-hemangioma-arterial anomalies-sternal cleft and supraumbilical raphe (PHACE) syndrome and over 90% had an accompanying cerebrovascular abnormality (Table 3), [30]. The segmental hemangioma may occur on the same side as the cerebrovascular abnormality [31]. Drolet and Frieden postulate that the primary defect in PHACE syndrome may relate to abnormal arterial development, leading to vascular insufficiency [23]. This localized hypoxic reaction may become the aggravating factor leading to segmental hemangioma development. This is different from the generalized hypoxic response experience in utero.

Clinical presentation
Infantile hemangioma presents in a variety of ways. It often appears in the first few weeks after birth [3]. The vascular tumors grow quickly during the first year and slowly regress over the next several years [32]. Over half of all IHs present as painless, superficial, bright red hemangiomas [18, 33-35]. As superficial hemangiomas involute, they change in color from bright red to violaceous to gray as the hemangioma flattens. Deep hemangiomas make up about 15% [33]. They present as bluish-to-flesh-colored swellings, depending on depth of the lesion. As deep hemangiomas involute, they lose the blue color. Mixed IH shares characteristics of both deep and superficial IH.

Table 3. *Syndromes associated with infantile hemangiomas.*

Associations	Abnormalities	References
PHACES	Posterior fossa malformations – Dandy walker syndrome, hypoplasia/agenesis of the cerebellum, supratentorial abnormalities	[33, 102, 103]
	Hemangiomas – large segmental hemangioma of the face including scalp	
	Arterial Anomalies – dysplasia of large cerebral arteries, aberrant course of large cerebral or cervical arteries	
	Cardiac defects – coarctation of the aorta, aberrant origin of the subclavian artery, pulmonary stenosis, aneurysm	
	Eye abnormalities – optic atrophy, cataracts, coloboma alterations of retinal vessels	
	Sternal cleft and supraumbilical raphe syndrome – sternal cleft, sternal pit, sternal defect	
PELVIS	Perineal hemangioma, external genitalia malformation, lipomylomeningoce, vesicorenal abnormalities, imperforate anus, skin tag	[33, 104]
LUMBAR	Lower body hemangioma	[105]
	Lipoma and other cutaneous anomalies – skin tag, sacral dimple, hair tuft, nevus	
	Urogenital anomalies – bladder extrophy, ureteral reflux, clitoromegaly, undescended tgestis, hydrocele	
	Ulceration	
	Myelopathy – tethered cord, lipomylelocele, lipomyelomeningocele, syrinx	
	Bony deformities – foot deformity, hip dysplasia, scoliosis	
	Anorectal anomalies – imperforate anus, deviated gluteal cleft	
	Arterial anomalies – dysplasia, narrowing, aberrant course/origin	
	Renal anomalies – single kidney, hydronephrosis, pelvic kidney	
SACRAL	Spinal dysraphism, anogenital, cutaneous, renal and urologic anomalies, associated with an angioma of lumbosacral localization	[106]

* It is important to note that PELVIS, LUMBAR and SACRAL may be variations of a single syndrome.

Infantile hemangioma can also be described in terms of pattern: focal, segmental, multifocal, or indeterminate [36]. Simply, focal hemangiomas appear to grow from a single, localized focus. Segmental lesions are found over a specific cutaneous region and may have plaque-like features. Infantile hemangioma is deemed multifocal if there are multiple, distinct, linear, non-contiguous papules and nodules. Indeterminate IH cannot be classified into localized or segmental groups. Differentiating IH based on morphology is important as segmental hemangiomas, regardless of size, are more likely to have other associated abnormalities.

The significant clinical presentations of IH, based on unique locations will be discussed below. Infantile hemangioma can be found in cutaneous or visceral locations [37]. Over 40% of cutaneous IHs appear on the face [36, 37]. Other locations include the trunk, extremities, and perineum. Visceral IH may involve the GI tract and liver [38].

Infantile hemangioma of the head and neck
Infantile hemangioma is most commonly found on the head and neck (Figure 1). This is significant because of the obvious disfigurement associated with ulceration and scarring [39]. Segmental IH is most likely to ulcerate at a median of 4 months in a large, multicenter prospective study [40]. Infantile hemangioma found on the nasal tip can lead to involvement of the underlying cartilage structure leading to serious deformities [41]. Some have **advocated for the use of the "nasal crease sign" to** predict nasal cartilage involvement and destruction [42]. Wright et al. describe a linear, gray atrophic crease that may appear in the inferior nasal columella prior to nasal collapse. Furthermore, the **"Cyano nose" appearance can have an immense** psychological impact on the patient [41]. Also, IH can rarely appear in the subglottic region, resulting in a high risk of functional impairment. The most feared complication of subglottic IH is airway obstruction

Figure 1. *Gross appearance of infantile hemangioma on the neck.*

[22]. Periocular IH is found on the orbit and eyelids. The most common complication is amblyopia, likely with lesions greater than 1cm [43, 44]. Other complications include strabismus and physical disfigurement [36].

Parotid infantile hemangioma
Parotid IH has been described as a painless, mobile mass in the peri-auricular or cervicofacial region that may be accompanied by a bluish hue [45, 46]. Complications range from ulceration and infection to airway obstruction in severe cases. One retrospective study found that 70% of parotid IH involved the ear [46]. Although reports of bilateral parotid IH are rare in the literature, the presence of such lesions could lead to hearing loss and speech impairment if persistent past one year.

Infantile hemangioma of the extremities
Classically, the large, segmental IH may be associated with PHACE or LUMBAR syndromes [47]. Recently, Weitz et al. characterized IH on the extremities using a retrospective, multicenter cohort study [47]. Nearly three-**fourths of cases followed a "biker glove"** distribution lacking involvement of the distal digits. Nearly a fifth of patients presented with IH with minimal or arrested growth (IH-MAG) and reticular pattern. Infantile hemangioma-MAG was defined as IH with a proliferative component spanning less than 25% of the surface area [15, 47]. Over half of patients with the IH-MAG, reticular pattern had complications such as ulceration [47]. In a single case report,

Mulliken et al. described the rare ventral-caudal anomalies and cardiac failure that tended to occur in six infants with reticular infantile hemangiomas of the extremities [13]. Ventral-caudal anomalies included omphalocele, recto-vaginal fistula, solitary/duplex kidney, imperforate anus, and tethered cord.

Lumbar infantile hemangioma
Lumbosacral IH (Table 3) are concerning when they appear as segmental lesions crossing the midline of the lumbosacral spine or gluteal cleft [48]. A multicenter, prospective cohort study found that in 51.2% of patients with such lesions greater than 2.5cm, spinal anomalies were present. These included tethering of the spinal cord, congenital lipomatous malformations, and intra-spinal hemangiomas.

Hepatic infantile hemangioma
Hepatic IH are often asymptomatic, present more frequently in females (3:1 ratio), and follow the typical growth pattern of IH [38, 49]. Most are clinically silent and accidently detected on routine imaging [49]. Thus, determining a true prevalence is difficult. However, some may become symptomatic and manifest as cardiac failure related to shunting, hypothyroidism owing to overproduction of type 3 iodothyronine deiodinase inactivating thyroid hormone, or intravascular consumptive coagulopathy [38, 50]. In one study based in two **tertiary childrens' hospitals, it was found that 51%** of infants had cardiac insufficiency and 15% presented with hypothyroidism [49].

Associated syndromes
There are several, overlapping syndromes associated with infantile hemangioma (Table 3).

Making the diagnosis and differential diagnosis
The diagnosis of infantile hemangioma is largely based on natural history, clinical presentation, and physical examination [51]. Diagnostic tests can be used if the diagnosis is unclear or if lesions are deep. They include MRI, Doppler studies, ultrasound, and platelet count [33]. Biopsy may produce a definitive diagnosis. However, it is uncommonly done as the clinical diagnosis is often adequate. The differential diagnosis of IH is discussed below.

Vascular malformation

With increased understanding of IH in the past few decades, more than 95% of vascular malformations and IH can be differentiated on physical exam and natural history alone [33, 51]. Vascular malformations are present at birth, grow with the child, and fail to regress [51]. The lymphatic subset of vascular malformations may be more difficult to differentiate from deep IH. Studies using ultrasound have been able to accurately differentiate between IH and vascular malformation with the presence of solid tissue mass in IH being strongest predicting factor [52].

Kaposiform hemangioendothelioma (KHE)

This is a rare, distinct entity occurring in the pediatric population and discussed in association with lymphangiomatosis, a condition of diffuse lymphatic malformations, or Kasabach-Merrit phenomenon (KMP), [53]. It occurs on the trunk, extremities, and retroperitoneum [54]. KHE is less commonly found on the cervicofacial region where IH is more likely found. KMP, not associated with IH, is described as a large, violaceous, vascular tumor with a triad of thrombocytopenia, localized intravascular coagulopathy, and bleeding [55]. Histologically, the tumor consists of slit like vessels with hemosiderin and fragmented erythrocytes lacking distinct capillaries [53]. Also, there are irregular lobules and sheets of cells in the dermis and subcutis with decreased pericytes and mast cells [54].

Tufted angioma

Tufted angiomas are pediatric vascular tumors appearing as erythematous, indurated plaques [56]. Tufted angiomas are thought to be on the same clinical spectrum as KHE [54]. Both tufted angiomas and KHE may be complicated by KMP; however, this complication is more likely to occur with KHE.

Port-wine stain (nevus flammeus)

Capillary malformations can be subdivided into the common nevus simplex and the uncommon port-wine stain. The former may be colloquially referred **to as a "salmon patch" or "stork bite." It often affects** the glabella, eyelids, forehead, and nape [57]. The port-wine stain is an uncommon congenital lesion, occurring in only 0.3% of healthy newborns [58]. It often appears with discrete, irregular borders in the distribution of the trigeminal nerve [59, 60]. Lesions may start as pink and flat but become darker and more nodular in adulthood [59]. They are permanent and do not involute. Port wine stains may be seen in conjunction with Sturge-Weber and von Hippel-Lindau disease.

Congenital hemangiomas

Congenital hemangiomas are solitary lesions fully present at birth as the proliferative phase is completed in utero [60]. Congenital hemangiomas are divided into non-involuting congenital hemangioma (NICH) and rapidly involuting congenital hemangioma (RICH), [3]. NICH lesions appear as solitary, pink-purple plaques, with surface telangiectasia located on the head, neck, trunk, and extremities [61]. NICH will not involute and may **show increased draining veins in the lesion's** periphery. RICH has many morphologic variants but may also be a bossed plaque or tumor. Involution often occurs completely in RICH leaving behind excess skin seen in the first 5-14 months. It is important to note that both RICH and NICH are GLUT1 negative [61].

Pyogenic granuloma

Pyogenic granulomas (PG) are proliferative, vascular lesions found on the skin or mucosae [62]. PG appears as a small, gray-brown mass on the face or upper trunk. It is often friable or ulcerated leading to repetitive bouts of bleeding [54, 62]. It presents in the second or third decade of life. Histologically, PG appears as capillaries in a unique lobular arrangement with small connecting arteries and veins. PG is seen in 2% of pregnant women, suggesting a hormonal basis [63].

Evolution without treatment

The natural history of IH is classically described as a rapid proliferative phase, followed by a slower late proliferative phase, a plateau phase, and, finally, gradual involution [64]. It is interesting to note that Tollefson and Frieden report about 65% of infants have visible hemangioma precursors on day one of life in a study examining serial photographs of infants with IH [64]. One study showed that 80% of IH growth is reached by 3 months and 80% of IH completed the early proliferative growth phase by 5 months [65]. It was also found that IH growth was

more rapid in weeks 1-8 compared to later months. Furthermore, the growth was non-linear, with growth most rapid between 5.5 and 7.5 weeks. Thus, many advocate for dermatology referral before the time period of greatest proliferation [66]. Tollefson and Frieden found that, on average, infants present to a pediatric dermatologist at age 5 months, when the majority of growth is finished and complications are inevitable [64].

Many IH will involute and resolve spontaneously, especially small or superficial hemangiomas. However, the complications of IH are feared and are important in choosing between watchful observation and active treatment.

Ulceration is the most common complication, occurring in 15-25% of IH [40, 67]. It is painful and may lead to scarring [37]. In a prospective, multicenter study of over 1,000 patients, Chamlin et al. found that 16% of ulcerated hemangiomas became infected and approximately 41% had the complication bleeding [40]. It was difficult to discern infection from colonization. However, cultures most commonly revealed *Pseudomonas sp.* and gram positive bacteria such as *Staphylococcus aureus.* Of the bleeding lesions, only one was significant enough to require transfusion. Ulceration often occurs in the proliferative phase, at about 2.6 months [68]. Maguiness et al. described the early white discoloration as a sign of impending ulceration. Other risk factors for ulceration include location on the lower lip, neck, perineal area, pressure points, and trauma [40]. Furthermore, Wright et al. presented a case series in which a linear gray, atrophic crease in the inferior nasal columella was seen prior to ulceration leading to nasal cartilage destruction [42]. Another rare complication, of about 1.4% incidence, is airway hemangioma leading to obstruction [69]. It may be seen in infants with **mandibular or "beard" pattern IH. The pattern is** described as spanning the bilateral peri-auricular region, chin, anterior neck, and lower lip. It often presents between ages 6-12 weeks as progressive, biphasic stridor. It may be confused for croup. However, patients are afebrile and the stridor does not resolve with time.

Periocular hemangioma may compromise visual development or cause amblyopia as a result of abnormal visual input [67, 70]. Haggstrom noted 5.6% of hemangiomas in a prospective, multicenter **cohort study to be "sight-threatening"** [37]. Complications include astigmatism, strabismus related to involvement of extra ocular muscles, and extension into the retrobulbular space [67, 70]. Complications are especially common with large hemangiomas. In fact, periocular hemangiomas greater than 1cm and those associated with PHACES syndrome were most likely to be associated with amblyopia (Table 3), [44].

Liver IH is a rare entity, possibly leading to high-risk complications. Multiple cutaneous hemangiomas, usually more than five, are associated with visceral involvement including the liver [71]. Some have recommended abdominal ultrasound screening for liver hemangioma in infants younger than 6 months and more than 5-6 cutaneous IH [71, 72]. Most liver hemangiomas are asymptomatic but some may present with high output cardiac failure or hypothyroidism [37, 73].

Treatment options
There are various treatment options for IH depending on size, type, and location. Prevention of permanent disfiguration, which may lead to psychosocial distress, is the most common reason to initiate therapy [32]. Intervention is sometimes sought in large, rapidly growing hemangiomas or those found in critical regions [37].

Active observation is the mainstay for the majority of small uncomplicated IH as most spontaneously involute. Treatment options can be divided into medical and procedural. Currently, propranolol, a non-selective beta-blocker, has become a mainstay of treatment. The U.S. Food and Drug Administration approved the use of propranolol in pediatrics for the treatment of infantile hemangiomas in 2014 [32, 74]. Leaute-Labreze et al. were the first to describe the use of propranolol in treating IH in nearly a dozen patients [75]. Within one day, the hemangiomas had changed from a deep purple to a lighter color and had a softer texture. The proposed mechanism is vasoconstriction and decreased expression of angiogenic factors. In a study of 55 patients,

propranolol caused improvement of IH in all but one patient, regardless of location, morphology, or size [76]. Another group used ultrasonography to objectively analyze the treatment of IH with oral propranolol [77]. Significant volume reduction was seen after 6-30 months of continuous treatment, with an average 47% decrease in volume. Rare but serious complications reported with use of oral propranolol include hypotension, bradycardia, bronchospasm, hypoglycemia, and hyperkalemia [74]. The consensus conference advocated for use of 1-3 mg/kg per day while tracking response to determine individual optimal doses. A response is often seen after three to four months of treatment but may be continued until the start of involution [32]. Furthermore, cessation of therapy prior to 6 months may lead to rebound growth. It has been proposed that propranolol treatment should be initiated before the proliferative growth phase of IH when irreversible changes may have occurred [64]. However, studies have shown positive outcomes in patients treated with the beta-blocker after the proliferative phase [78, 79]. The authors suggest that efficacy of propranolol is not limited to antiproliferative effect but may relate to apoptosis and vasoconstriction after the proliferative phase [80].

A randomized clinical trial compared the use of atenolol, a cardioselective beta-blocker, to propranolol for treatment of IH [81]. Atenolol was found to be comparable to propranolol in both efficacy and safety. The selectivity of atenolol makes it a more appropriate medication for asthmatic patients.

Many have advocated for the use of topical timolol, in an effort to lower risk of adverse effects in comparison to systemic propranolol. This treatment is preferred for those with small, superficial IH [82]. Khunger and Pahwa described a case of an 18-month-old female with PHACES syndrome who exhibited dramatic resolution of a large, ulcerated IH spanning the entire right face and involving the peri-orbital area [83]. The patient was treated with ten drops of topical 0.5% timolol ophthalmic solution twice daily. The patient showed near complete resolution of the IH at eight weeks with only pruritus

reported as an adverse effect. A large, multi-center retrospective study concluded topical timolol therapy to be efficacious in superficial IH with thickness less than 1mm, despite pre-treatment size [84]. However, authors noted that in cases in which IH continues to progress despite topical timolol therapy, systemic treatment should be pursued. A recent prospective trial measured plasma levels of timolol after topical administration of the medication for IH treatment. The study failed to show adverse events after topical application of timolol even with higher doses resulting in plasma levels between 0.3-1.6 ng/mL [85]. Timolol may be used topically after oral propranolol is discontinued as maintenance therapy and to prevent rebound. Topical timolol may be an alternative to active observation when parents desire treatment.

Another common medical approach to IH is oral corticosteroid treatment, especially when beta-blockers are contraindicated or for complicated IH. Regimens between 1-5 mg/kg per day have been used and have shown good efficacy [86]. One meta-analysis reported a mean prednisone dose of 2.9 mg/kg given for nearly 2 months before tapering had an 84% response rate [86]. A multicenter, retrospective chart review found that propranolol was far more efficacious and had less risk of adverse complications in comparison to oral corticosteroids in treating IH [78]. The oral corticosteroid arm was made up of 42 patients and 100% of them had one or more adverse effects. All patients had Cushingoid features, four had gastroesophageal reflux, two had hypertension, and one had an arterial bleed related to ulceration and erosion of the external carotid artery requiring life-saving surgery. In the propranolol group, there were few adverse events. One patient experienced hypoglycemia and two patients experienced a non-specific skin eruption, not associated with the treatment. It should be emphasized that because of adverse events, many physicians have veered from use of corticosteroids to treat IH.

Other medical treatments of IH have largely fallen out of favor including interferon-α and vincristine. Interferon-α, a potent inhibitor of angiogenesis, has been associated with spastic diplegia, occurring in

2.5% of patients [87]. Other complications ranged from flu-like illness to seizures [87, 88]. Vincristine is a vinca-alkaloid interfering with mitotic spindle microtubules. It has been used to treat lymphoma and solid tumors [89, 90]. Vincristine has been successfully used to treat high-risk IH after failure of corticosteroid or interferon-**α therapy** [90, 91]. However, side effects include alopecia, peripheral neuropathy, paresthesias, leukopenia, anemia, and abdominal pain.

Intralesional and topical treatments have been used and preferred owing to less systemic side effects. However, the evidence for these treatments is limited. One study has shown the efficacy of combining betamethasone dipropionate injection with oral propranolol [92]. The corticosteroid injection reduced rapid tumor growth. It also increased tumor mast cells leading to increased apoptosis of endothelial cells. Intra-lesional corticosteroids have especially been used by ophthalmologists to treat periocular hemangiomas. However, complications have included eyelid necrosis and central retinal artery occlusion [93]. Topical 5% imiquimod has been used successfully in treating infantile hemangiomas [94, 95].

An extensive meta-analysis of 13 studies examined the efficacy of using pulsed dye laser (PDL) therapy in treating infantile hemangioma [96]. Improvement of infantile hemangioma appearance was seen in all studies with a lesion regression rate of 89.1%. However, 6.2% of patients had adverse events including ulceration, bleeding, hyperpigmentation, textural changes, and atrophic scars. The effect of PDL is superficially limited to a depth of 1-2mm; thus, it is not as beneficial in mixed or deep IH. One randomized clinical trial studied the efficacy of PDL in infants with superficial, uncomplicated IH in the pre-proliferative or early proliferative phase [97]. They did not recommend using PDL in uncomplicated, superficial hemangiomas. This is because of the likelihood of natural, spontaneous involution and increased risk of atrophic scars and hypopigmentation with treatment. Some experts believe that PDL should only be used in superficial IH accompanied by residual telangiectasia or ulceration once involution has actually started [71, 98]. There is much debate as to which IH will benefit from PDL and which settings are the most appropriate for treatment.

Surgical excision is a definitive option in treating IH. Indications include incomplete resolution, severe disfiguration, or lesions in the periorbital region, nose, airway, or ear canal [98]. Patients with cervicofacial hemangiomas, especially involving the lip, eye, or nose were seen as good candidates for total excision [99]. In a retrospective study, 99.5% of patients who underwent surgery had improved facial contours and volume reduction. Surgical excision may offer low risk to benefit ratio in select patients with periocular tumors [100]. Alternatively, some experts advocate for confirmation of IH via GLUT1 marker and preoperative treatment with propranolol to shrink the lesion prior to surgical excision [101].

Thus, it is obvious that management options of IH vary and include active observation, topical and intralesional treatments, medical management, and surgical procedures. Each patient should receive an individualized approach as different treatment options are appropriate depending on a variety of patient factors.

Discussion
Reappraisal
After conducting a critical review of the literature, we believe that IH should be treated in certain situations: 1) risk of cosmetic disfiguration, most likely involving the face, 2) risk of vital organ compromise, 3) failure to regress as predicted by natural history. Most IH will naturally regress in the first few years of life, without need for intervention. However, we advocate for dermatologic consultation in the first few weeks of life, especially for IHs in critical locations or those which may lead to functional compromise, as this is thought to be the period of greatest proliferation of the lesions and intervention at this time may prevent irreversible changes and assessment for associations is required. During this initial visit, the individual risks and benefits of active observation versus treatment can be discussed with the parents. It is important to

remember that intervention itself can lead to complications including scarring and disfigurement.

On the other hand, lesions that are located in critical areas can cause a myriad of complications including ulceration, infection, bleeding, airway compromise, visual disturbances, and even high output cardiac failure. These lesions should be managed medically or surgically depending on location and size of the lesion. The literature has shown great efficacy of propranolol as first line, medical treatment. Other options including corticosteroids and immunomodulator therapies have significant side effect profiles. Furthermore, more invasive procedures, such as PDL or surgical excision, should be limited to cases in which propranolol has failed or IH is present in critical locations.

Thus, we advocate for an individualized management approach for each patient. Parents should seek medical consultation in the first few weeks of life; this is the time of greatest proliferation. Infantile hemangioma that has a risk of cosmetic disfiguration or is in a critical location, possibly leading to functional compromise, such as the peri-orbital space, lip, or visceral organs should be immediately treated. However, most IH is uncomplicated and can be actively observed up to 12-18 months of life.

Conclusion

Infantile hemangiomas are the most common vascular tumors of infancy. Historically, there has been much confusion regarding classification of IH. Today, we follow the standardized classification of the ISSVA, which is based on pattern, depth, associations with other lesions, and immunohistochemical markers. Currently, the most important marker to accurately diagnose IH is GLUT1.

Infantile hemangioma is commonly diagnosed clinically based on natural history of the lesion. Most IH appears on the head and neck where potential complications range from cosmetic disfiguration to airway obstruction. However, other locations of IH include the extremities, trunk, and visceral organs with each location having unique, associated complications.

In the case of IH treatment, patients should receive individualized approaches, with risks and benefits carefully taken into consideration. Infantile hemangioma in high-risk locations, such as peri-orbital, airway, and the liver, are more likely to be treated as benefit of treatment likely outweighs the risks. Overall, greater awareness about infantile hemangiomas, their associations, and available management options is needed.

References

1. Kilcline C, Frieden IJ. Infantile hemangiomas: how common are they? A systematic review of the medical literature. *Pediatr Dermatol.* 2008;25(2):168-73. [PMID: 18429772].
2. Drolet BA, Esterly NB, Frieden IJ. Hemangiomas in children. *N Engl J Med.* 1999;341(3):173-81. [PMID: 1040385].
3. Mulliken JB, Enjolras O. Congenital hemangiomas and infantile hemangioma: missing links. *J Am Acad Dermatol.* 2004;50(6):875-82
4. Bowers R, Graham E, Tomlinson K. The natural history of the strawberry nevus. *Arch Dermatol.* 1960;82(5):667-80. [PMID: 15153887].
5. Bauland CG, Lüning TH, Smit JM, Zeebregts CJ, Spauwen PH. Untreated hemangiomas: growth pattern and residual lesions. *Plast Resconstr Surg.* 2011;127(4):1643-8. [PMID: 21460670].
6. Jinnin M, Ishihara T, Boye E, Olsen BR. Recent progress in studies of infantile hemangioma. *J Dermatol.* 2010;37(4):283-98. [PMID: 21218607].
7. Lister W. The natural history of strawberry naevi. *Lancet.* 1938;231(5991):1429-34.
8. Patterson A. Spontaneous cure of a naevus maternus—large vascular tumor occupying side of neck. *South Med Rec.*
1894:24:477
9. Mulliken JB, Glowacki J. Hemangiomas and vascular malformations in infants and children a classification based on endotbelial characteristics. *Plast Reconstr Surg, l982.*69(3):t4l2-422. [PMID: 7063565].
10. Rydh M, Malm M, Jernbeck J, Dalsgaard C-J. Ectatic blood vessels in port-wine stains lack innervation: possible role in pathogenesis. *Plast Reconstr Surg.* 1991;87(3):419-22. [PMID: 1825517].
11. Enjolras O. Classification and management of the various superficial vascular anomalies: hemangiomas and vascular malformations. *J Dermatol.* 1997;24(11):701-10. [PMID: 9433027].
12. Wassef M, Blei F, Adams D, Alomari A, Baselga E, et al. Vascular anomalies classification: recommendations from the International Society for the Study of Vascular Anomalies. *Pediatrics.* 2015;136(1):e203-e14. [PMID: 26055853].
13. Mulliken JB, Marler JJ, Burrows PE, Kozakewich HP. Reticular Infantile Hemangioma of the Limb Can Be Associated with Ventral-Caudal Anomalies, Refractory Ulceration, and Cardiac Overload. *Pediatr Dermatol.* 2007;24(4):356-62. [PMID: 17845155].
14. Bessis D, Bigorre M, Labrèze C. Reticular infantile hemangiomas with minimal or arrested growth associated with lipoatrophy. *J*

Am Acad Dermatol. 2015;72(5):828-33. [PMID: 25766364].

15. Suh K-Y, Frieden IJ. Infantile hemangiomas with minimal or arrested growth: a retrospective case series. *Arch Dermatol.* 2010;146(9):971-6.

16. Martinez-Perez D, Fein NA, Boon LM, Mulliken JB. Not all hemangiomas look like strawberries: uncommon presentations of the most common tumor of infancy. *Pediatr Dermatol.* 1995;12(1):1-6. [PMID: 20855695].

17. Bourrat E, Lemarchand-Venencie F, Jacquemont M-L, El Ghoneimi A, Wassef M, et al. PELVIS/SACRAL syndrome with livedoid hemangioma and amniotic band. *Annals Dermatol Vener.* 2008; 135(12):855-9. [PMID: 19084698].

18. Léauté-Labrèze C, Prey S, Ezzedine K. Infantile haemangioma: part I. Pathophysiology, epidemiology, clinical features, life cycle and associated structural abnormalities. *J Eur Acad Dermatol Venereol.* 2011;25(11):1245-53. [PMID: 21569112].

19. Drolet BA, Swanson EA, Frieden IJ. Infantile hemangiomas: an emerging health issue linked to an increased rate of low birth weight infants. *J Pediatr.* 2008;153(5):712-5. [PMID: 18940356].

20. Walter JW, Blei F, Anderson JL, Orlow SJ, Speer MC, et al. Genetic mapping of a novel familial form of infantile hemangioma. *Am J Med Genet A.* 1999;82(1):77-83. [PMID: 9916848].

21. Bauland CG, Smit JM, Bartelink LR, Zondervan HA, Spauwen PH. Hemangioma in the newborn: increased incidence after chorionic villus sampling. *Prenat Diagn.* 2010;30(10):913-7. [PMID: 20824891].

22. Haggstrom AN, Drolet BA, Baselga E, Chamlin SL, Garzon MC, et al. Prospective study of infantile hemangiomas: demographic, prenatal, and perinatal characteristics. *J Pediatr.* 2007;150(3):291-4. [PMID: 17307549].

23. Drolet BA, Frieden IJ. Characteristics of infantile hemangiomas as clues to pathogenesis: does hypoxia connect the dots? *Arch Dermatol.* 2010;146(11):1295-9. [PMID: 21079070].

24. Kleinman ME, Greives MR, Churgin SS, Blechman KM, Chang EI, et al. Hypoxia-induced mediators of stem/progenitor cell trafficking are increased in children with hemangioma. *Arterioscler Thromb, Vasc Biol.* 2007;27(12):2664-70. [PMID: 17872454].

25. North PE, Waner M, Mizeracki A, Mihm MC. GLUT1: a newly discovered immunohistochemical marker for juvenile hemangiomas. *Hum Pathol.* 2000;31(1):11-22. [PMID: 10665907].

26. North PE, Waner M, James CA, Mizeracki A, Frieden IJ, et al. Congenital nonprogressive hemangioma: a distinct clinicopathologic entity unlike infantile hemangioma. *Arch Dermatol.* 2001;137(12):1607-20. [PMID: 11735711].

27. Mobasheri A, Richardson S, Mobasheri R, Shakibaei M, Hoyland J. Hypoxia inducible factor-1 and facilitative glucose transporters GLUT1 and GLUT3: putative molecular components of the oxygen and glucose sensing apparatus in articular chondrocytes. *Histol Histopathol.* 2005;20(4):1327-38. [PMID: 16136514].

28. North PE, Waner M, Mizeracki A, Mrak RE, Nicholas R, et al. A unique microvascular phenotype shared by juvenile hemangiomas and human placenta. *Arch Dermatol.* 2001;137(5):559-70. [PMID: 11346333].

29. Ritter MR, Dorrell MI, Edmonds J, Friedlander SF, Friedlander M. Insulin-like growth factor 2 and potential regulators of hemangioma growth and involution identified by large-scale expression analysis. *Proc Natl Acad of Sci.* 2002;99(11):7455-60. [PMID: 12032304].

30. Haggstrom AN, Garzon MC, Baselga E, Chamlin SL, Frieden IJ, et al. Risk for PHACE syndrome in infants with large facial hemangiomas. *Pediatr.* 2010:peds. 2009-3166. [PMID: 20643720].

31. Hess CP, Fullerton H, Metry D, Drolet B, Siegel D, et al. Cervical and intracranial arterial anomalies in 70 patients with PHACE syndrome. *Am J Neuroradiol.* 2010;31(10):1980-6. [PMID: 20705698].

32. Darrow DH, Greene AK, Mancini AJ, Nopper AJ. Diagnosis and management of infantile hemangioma. *Pediatrics.* 2015;136(4):e1060-e104. [PMID: 26416931].

33. Frieden IJ, Eichenfield LF, Esterly NB, Geronemus R, Mallory SB. Guidelines of care for hemangiomas of infancy. *J Am Acad Dermatol.* 1997;37(4):631-7. [PMID: 9344205].

34. Torres EB, Wittel JB, van Esso Arbolave DL, Bosch MIF, Sanz ÁC, et al. Spanish consensus on infantile haemangioma. *An Pediatr.* 2016;85(5):256-65

35. Callahan AB, Yoon MK. Infantile hemangiomas: A review. *Saudi J Ophthalmol.* 2012;26(3):283-91. [PMID: 26776166].

36. Chiller KG, Passaro D, Frieden IJ. Hemangiomas of infancy: clinical characteristics, morphologic subtypes, and their relationship to race, ethnicity, and sex. *Arch Dermatol.* 2002;138(12):1567-76. [PMID: 12472344].

37. Haggstrom AN, Drolet BA, Baselga E, Chamlin SL, Garzon MC, et al. Prospective study of infantile hemangiomas: clinical characteristics predicting complications and treatment. *Pediatrics.* 2006;118(3):882-7. [PMID: 16950977].

38. Stanley P, Geer GD, Miller JH, Gilsanz V, Landing BH, et al. Infantile hepatic hemangiomas. Clinical features, radiologic investigations, and treatment of 20 patients. *Cancer.* 1989;64(4):936-49. [PMID: 2663135].

39. Huoh KC, Rosbe KW. Infantile hemangiomas of the head and neck. *Pediatr Clin North Am.* 2013;60(4):937-49. [PMID: 23905829].

40. Chamlin SL, Haggstrom AN, Drolet BA, Baselga E, Frieden IJ, et al. Multicenter prospective study of ulcerated hemangiomas. *J Pediatr.* 2007;151(6):684-9. [PMID: 18035154].

41. Hamou C, Diner PA, Dalmonte P, Vercellino N, Soupre V, et al. Nasal tip haemangiomas: Guidelines for an early surgical approach. *J Plast, Reconstr Aesthet Surg.* 2010;63(6):934-9. [PMID: 19540825].

42. Dakara RW, Daniela CR, Anthony JM, Sarah LC, Annette MW. The nasal crease sign in segmental facial hemangioma—an early sign of cartilage destruction. *Pediatr Dermatol.* 2007;24(3):241-5. [PMID: 17542872].

43. Robb RM. Refractive errors associated with hemangiomas of the eyelids and orbit in infancy. *Am J Ophthalmol.* 1977;83(1):52-8. [PMID: 835667].

44. Schwartz SR, Blei F, Ceisler E, Steele M, Furlan L, et al. Risk factors for amblyopia in children with capillary hemangiomas of the eyelids and orbit. *J AAPOS.* 2006;10(3):262-8. [PMID: 16814181].

45. Crow E, Kang TL. Point-of-Care Ultrasound to Diagnose Infantile Parotid Hemangioma. *Pediatr Emerg Care.* 2016;32(11):812-4. [PMID: 26569077].

46. Greene AK, Rogers GF, Mulliken JB. Management of parotid hemangioma in 100 children. *Plast Reconstr Surg.* 2004;113(1):53-60. [PMID: 14707622].

47. **Weitz NA, Bayer ML, Baselga E, Torres M, Siegel D, et al. The "biker-glove" pattern of segmental infantile hemangiomas on the hands** and feet. *J Am Acad Dermatol.* 2014;71(3):542-7. [PMID: 24929885].

48. Drolet BA, Chamlin SL, Garzon MC, Adams D, Baselga E, et al. Prospective study of spinal anomalies in children with infantile hemangiomas of the lumbosacral skin. *J Pediatr.* 2010;157(5):789-94. [PMID: 20828712].

49. Kassarjian A, Zurakowski D, Dubois Je, Paltiel HJ, Fishman SJ, et al. Infantile hepatic hemangiomas: clinical and imaging findings and their correlation with therapy. *AJR Am J Roentgenol.* 2004;182(3):785-95. [PMID: 14975986].

50. Christison-Lagay ER, Burrows PE, Alomari A, Dubois J, Kozakewich HP, et al. Hepatic hemangiomas: subtype classification and

development of a clinical practice algorithm and registry. *J Pediatr Surg.* 2007;42(1):62-8. [PMID: 17208542].

51. Finn MC, Glowacki J, Mulliken JB. Congenital vascular lesions: clinical application of a new classification. *J Pediatr Surg.* 1983;18(6):894-900. [PMID: 6663421].

52. Paltiel HJ, Burrows PE, Kozakewich HP, Zurakowski D, Mulliken JB. Soft-tissue vascular anomalies: utility of US for diagnosis. *Radiology.* 2000;214(3):747-54. [PMID: 10715041].

53. Zukerberg LR, Nickoloff BJ, Weiss SW. Kaposiform hemangioendothelioma of infancy and childhood. An aggressive neoplasm associated with Kasabach-Merritt syndrome and lymphangiomatosis. *Am J Surg Pathol.* 1993;17(4):321-8. [PMID: 8494101].

54. Gampper TJ, Morgan RF, Bartlett SP. Vascular anomalies: hemangiomas. *Plast Reconstr Surg.* 2002;110(2):572-86. [PMID: 12142679].

55. Sarkar M, Mulliken JB, Kozakewich H, Robertson RL, Burrows PE. Thrombocytopenic coagulopathy (Kasabach-Merritt phenomenon) is associated with Kaposiform hemangioendothelioma and not with common infantile hemangioma. *Plast Reconstr Surg.* 1997;100(6):1377-86. [PMID: 9385948].

56. Bernstein EF, Kantor G, Howe N, Savit RM, Koblenzer PJ, et al. Tufted angioma of the thigh. *J Am Ac Dermatol.* 1994;31(2):307-11. [PMID: 8034793].

57. Juern AM, Glick ZR, Drolet BA, Frieden IJ. Nevus simplex: a reconsideration of nomenclature, sites of involvement, and disease associations. *J Am Acad Dermatol.* 2010;63(5):805-14. [PMID: 20728246].

58. Jacobs AH, Walton RG. The incidence of birthmarks in the neonate. *Pediatrics.* 1976;58(2):218-22. [PMID: 951136].

59. Esterly NB. Cutaneous hemangiomas, vascular stains and malformations, and associated syndromes. *Curr Probl Pediatr.* 1995;7(3):69-107. [PMID: 8932511].

60. Niechajev I, Clodius L. Histology of port-wine stain. *Eur J Plast Surg.* 1990;13(2):79-85

61. Krol A, MacArthur CJ. Congenital hemangiomas: rapidly involuting and noninvoluting congenital hemangiomas. *Arch Facial Plast Surg.* 2005;7(5):307-11. [PMID: 16172338].

62. Mills SE, Cooper PH, Fechner RE. Lobular capillary hemangioma: the underlying lesion of pyogenic granuloma. A study of 73 cases from the oral and nasal mucous membranes. *Am J Surg Pathol.* 1980;4(5):470-9. [PMID: 7435775].

63. Winton GB, Lewis CW. Dermatoses of pregnancy. *J Am Acad Dermatol.* 1982;6(6):977-98. [PMID: 7047596].

64. Tollefson MM, Frieden IJ. Early growth of infantile hemangiomas: what parents' photographs tell us. *Pediatrics.* 2012;130(2):e314-e20. [PMID: 22826568].

65. Chang LC, Haggstrom AN, Drolet BA, Baselga E, Chamlin SL, et al. Growth characteristics of infantile hemangiomas: implications for management. *Pediatrics.* 2008;122(2):360-7. [PMID: 18676554].

66. Zheng JW, Zhang L, Zhou Q, Mai HM, Wang YA, et al. A practical guide to treatment of infantile hemangiomas of the head and neck. *Int J Clin Exp Med.* 2013;6(10):851. [PMID: 24260591].

67. Frieden IJ, Haggstrom AN, Drolet BA, Mancini AJ, Friedlander SF, et al. Infantile hemangiomas: current knowledge, future directions. Proceedings of a research workshop on infantile hemangiomas. *Pediatr Dermatol.* 2005;22(5):383-406. [PMID: 16190987].

68. Maguiness SM, Hoffman WY, McCalmont TH, Frieden IJ. Early white discoloration of infantile hemangioma: a sign of impending ulceration. *Arch Dermatol.* 2010;146(11):1235-9. [PMID: 21079059].

69. Orlow SJ, Isakoff MS, Blei F. Increased risk of symptomatic hemangiomas of the airway in association with cutaneous hemangiomas in a "beard" distribution. *J Pediatr.* 1997;131(4):643-6. [PMID: 9386676].

70. Ni N, Guo S, Langer P. Current concepts in the management of periocular infantile (capillary) hemangioma. *Curr Opin Ophthalmol.* 2011;22(5):419-25. [PMID: 21730838].

71. Metry DW. Ten lessons learned from a hemangioma clinic.Semin Plast Surg; 2006: Thieme Medical Publishers.

72. Horii KA, Drolet BA, Frieden IJ, Baselga E, Chamlin SL, et al. Prospective study of the frequency of hepatic hemangiomas in infants with multiple cutaneous infantile hemangiomas. *Pediatr Dermatol.* 2011;28(3):245-53. [PMID: 21517952].

73. Storch C, Hoeger P. Propranolol for infantile haemangiomas: insights into the molecular mechanisms of action. *Br J Dermatol.* 2010;163(2):269-74. [PMID: 20456345].

74. Drolet BA, Frommelt PC, Chamlin SL, Haggstrom A, Bauman NM, et al. Initiation and use of propranolol for infantile hemangioma: report of a consensus conference. *Pediatrics.* 2013;131(1):128-40. [PMID: 23266923].

75. Léauté-Labrèze C, de la Roque ED, Hubiche T, Boralevi F, Thambo J-B, et al. Propranolol for severe hemangiomas of infancy. *New Engl J Med.* 2008;358(24):2649-51. [PMID: 18550886].

76. Schupp CJ, Kleber JB, Günther P, Holland-Cunz S. Propranolol therapy in 55 infants with infantile hemangioma: dosage, duration, adverse effects, and outcome. *Pediatr Dermatol.* 2011;28(6):640-4. [PMID: 21995836].

77. Rotter A, Samorano LP, Oliveira Labinas GH, Alvarenga JG, Rivitti-Machado MC, et al. Ultrasonography as an objective tool for assessment of infantile hemangioma treatment with propranolol. *Int J Dermatol.* 2017;56(2):190-4. [PMID: 27813086].

78. Price CJ, Lattouf C, Baum B, McLeod M, Schachner LA, et al. Propranolol versus corticosteroids for infantile hemangiomas: a multicenter retrospective analysis. *Arch Dermatol.* 2011;147(12):1371-6. [PMID: 21844428].

79. Zvulunov A, McCuaig C, Frieden IJ, Mancini AJ, Puttgen KB, et al. Oral propranolol therapy for infantile hemangiomas beyond the proliferation phase: a multicenter retrospective study. *Pediatr Dermatol.* 2011;28(2):94-8. [PMID: 21362031].

80. Izadpanah A, Kanevsky J, Belzile E, Schwarz K. Propranolol versus corticosteroids in the treatment of infantile hemangioma: a systematic review and meta-analysis. *Plast Reconstr Surg.* 2013;131(3):601-13. [PMID: 23142941].

81. Abarzúa-Araya Á, Navarrete-Dechent CP, Heusser F, Retamal J, Zegpi-Trueba MS. Atenolol versus propranolol for the treatment of infantile hemangiomas: a randomized controlled study. *J Am Acad Dermatol.* 2014;70(6):1045-9. [PMID: 24656727].

82. Pope E, Chakkittakandiyil A. Topical timolol gel for infantile hemangiomas: a pilot study. *Arch Dermatol.* 2010;146(5):564-5. [PMID: 20479314].

83. Khunger N, Pahwa M. Dramatic response to topical timolol lotion of a large hemifacial infantile haemangioma associated with PHACE syndrome.*Br J Dermatol.* 2011;164(4):886-8. [PMID: 21158749].

84. Püttgen K, Lucky A, Adams D, Pope E, McCuaig C, et al. Topical timolol maleate treatment of infantile hemangiomas. *Pediatrics.* 2016:e20160355. [PMID: 27527799].

85. Borok J, Gangar P, Admani S, Proudfoot J, Friedlander S. Safety and efficacy of topical timolol treatment of infantile haemangioma: A prospective trial. *Br J Dermatol.* 2018. [PMID: 28771668].

86. Bennett ML, Fleischer Jr AB, Chamlin SL, Frieden IJ. Oral corticosteroid use is effective for cutaneous hemangiomas: an

evidence-based evaluation.*Arch Dermatol.* 2001;137(9):1208-13. [PMID: 11559219].

87. Michaud AP, Bauman NM, Burke DK, Manaligod JM, Smith RJ. Spastic Diplegia and Other Motor Disturbances in Infants Receiving Interferon-Alpha. *Laryngoscope.* 2004;114(7):1231-6. [PMID: 15235352].

88. Bauman NM, Burke DK, Smith RJ. Treatment of massive or life-**threatening hemangiomas with recombinant α2a**-interferon. *Otolaryngol Head Neck Surg.* 1997;117(1):99-110. [PMID: 9230332].

89. Haisley-Royster C, Enjolras O, Frieden IJ, Garzon M, Lee M, et al. Kasabach-Merritt phenomenon: a retrospective study of treatment with vincristine. *J Pediatr Hematol Oncol.* 2002;24(6):459-62. [PMID: 12218593].

90. Wharton S, Soueid A, Nishikawa H, Sridhar A. Endangering cutaneous infantile hemangioma treated with vincristine: a case report. *Eur J Plast Surg.* 2009;32(3):157-61

91. Enjolras O, Breviere G, Roger G, Tovi M, Pellegrino B, et al. Vincristine treatment for function-and life-threatening infantile hemangioma.*Arch Pediatr.* 2004;11(2):99-107. [PMID: 14761730].

92. Shao R, Zhao D, Li J. Treatment of infantile hemangioma by intralesional injection of propranolol combined with compound betamethasone. *Eur Rev Med Pharmacol Sci.* 2016;20(4):751-5. [PMID: 26957280].

93. Sutula FC, Glover AT. Eyelid necrosis following intralesional corticosteroid injection for capillary hemangioma. *Ophthalmic Surgery, Lasers and Imaging Retina.* 1987;18(2):103-5. [PMID: 3574861].

94. Martinez MI, Sanchez-Carpintero I, North PE, Mihm MC. Infantile hemangioma: clinical resolution with 5% imiquimod cream. *Arch Dermatol.* 2002;138(7):881-4. [PMID: 12071813].

95. Barry R, Hughes B, Cook L. Involution of infantile haemangiomas after imiquimod 5% cream. *Clinic Exp Dermatol.* 2008;33(4):446-9. [PMID: 18485022].

96. Shen L, Zhou G, Zhao J, Li P, Xu Q, et al. Pulsed dye laser therapy for infantile hemangiomas: a systemic review and meta-analysis.*QJM.* 2014;108(6):473-80. [PMID: 25376585].

97. Batta K, Goodyear HM, Moss C, Williams HC, Hiller L, et al. Randomised controlled study of early pulsed dye laser treatment of uncomplicated childhood haemangiomas: results of a 1-year analysis. *Lancet.* 2002;360(9332):521-7. [PMID: 12241656].

98. Dinehart SM, Kincannon J, Geronemus R. Hemangiomas: evaluation and treatment. *Dermatol Surg.* 2001;27(5):475-85. [PMID: 11359498].

99. Goldenberg DC, Hiraki PY, Marques TM, Koga A, Gemperli R. Surgical treatment of facial infantile hemangiomas: An analysis based on tumor characteristics and outcomes. *Plast Reconstr Surg.* 2016;137(4):1221-31. [PMID: 26761514].

100. Deans RM, Harris GJ, Kivlin JD. Surgical dissection of capillary hemangiomas: an alternative to intralesional corticosteroids. *Arch Ophthalmol.* 1992;110(12):1743-7. [PMID: 1463416].

101. Pavlidis L, Spyropoulou GA, Michalopoulos N, Demiri E. Surgical Treatment of Facial Infantile Hemangiomas: An Analysis Based on Tumor Characteristics and Outcomes. *Plast Reconstr Surg.* 2016;138(5):947e-8e. [PMID: 27400433].