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REVIEW ARTICLE

# Infantile Hemangiomas

## An Update

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**Abstract** Infantile hemangioma (IH) is a common vascular tumor of infancy. Although benign, infants with IH can experience complications including ulceration, visual and airway impairment, and residual scarring and disfigurement. It is often challenging for clinicians to predict which tumors are in need of systemic treatment. However, data from various demographic and other studies have revealed further insights into this tumor. This article reviews the identification, evaluation, and management of high-risk IHs, including the indications for treatment and the use of systemic treatments such as corticosteroids, β-blockers, and vincristine.

## 1 Introduction

### 1.1 Epidemiology and Demographics

Infantile hemangioma (IH) is the most common, benign, soft tissue tumor of infancy with a reported incidence of 5–10 % [1]. The precise incidence of IH is difficult to ascertain as other vascular anomalies had been misclassified under IH's nomenclature prior to improvements in diagnostic criteria and capabilities. Morphologic variation in hemangioma lesions has muddled this distinction as well. Differential diagnoses include congenital hemangiomas (non-involuting congenital hemangioma, or NICH, and rapidly involuting congenital hemangioma, or RICH), which can be distinguished from IH by their presence at birth. Furthermore, congenital hemangiomas do not grow postnatally. Congenital hemangiomas can be detected by prenatal ultrasound and do not stain with the immunohistochemical marker, glucose transporter-1 (GLUT-1) [see Sect. 1.3]. Various demographic studies have revealed many insights into IHs. The tumor occurs at a higher frequency in female infants (ratio 2–3:1) and ethnic predilection for Caucasian infants is also well known [2, 3]. Additional associated risk factors include low birth weight, prematurity, and products of multiple gestation [2, 4]. Prenatal risk factors found to be linked to IH include advanced maternal age, pre-eclampsia, and placenta previa [2]. Regarding family history, in one study, 12 % of 1058 children with IH was reported to have a first-degree relative with a hemangioma [2].

### 1.2 Clinical Manifestations

IHs begin to appear during the first few weeks of life either as a telangiectatic patch or an area of pallor. The evolution of IH varies and can either change into small, bright red lesions or large, bulky tumors. The heterogeneous nature of IHs is often described by three clinical morphologies: (1) superficial; (2) deep; and (3) mixed [3, 5, 6]. Superficial hemangiomas present with a bright red color and are located at the superficial dermis. Deep hemangiomas involve the deep dermis and subcutis and appear as blue or skin-colored nodules. Mixed hemangiomas have components of both superficial and deep IHs. Another way that IHs has been subclassified is localized/focal, segmental, or indeterminate [5, 6]. Localized lesions are discrete and oval/round (Fig. 1) whereas segmental IHs extend across a large anatomic region and have

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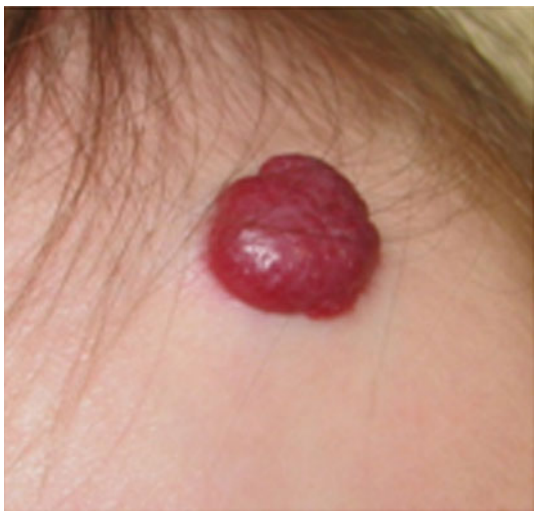

**Fig. 1** Localized/focal superficial infantile hemangioma

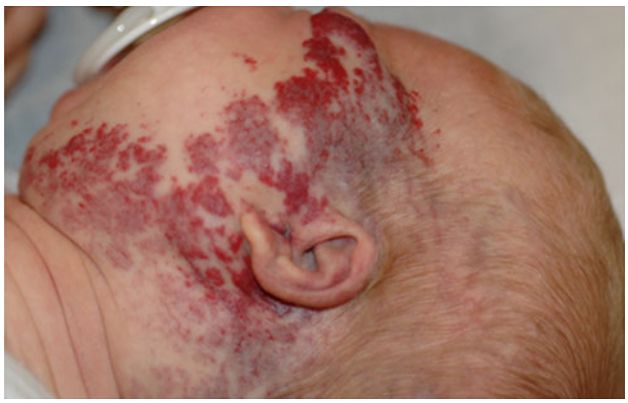

**Fig. 2** Segmental infantile hemangioma in infant with PHACE syndrome

a geographic shape (Fig. 2). Segmental lesions are typically at higher risk for complications [7].

The characteristic life cycle of IH makes it a unique childhood tumor. The biologic behavior of IH is subdivided into three phases, the first being a period of proliferation marked by rapid growth starting at 2–3 weeks of life and arresting at approximately 5–9 months of age [8]. The second or plateau phase, occurs thereafter with minimal change in growth, color, or size. Finally, the tumor spontaneously regresses in its involutional phase, starting at around 12 months and lasting up until 5–10 years of age. During the last phase, the lesion usually becomes soft and undergoes a change in color from bright red to purple/gray. Of note, both the rate and duration of growth and involution is highly variable. Although most tumors naturally involute, lesions can result in permanent residual changes including fibro-fatty residuum (Fig. 3), scarring, and telangiectasias.

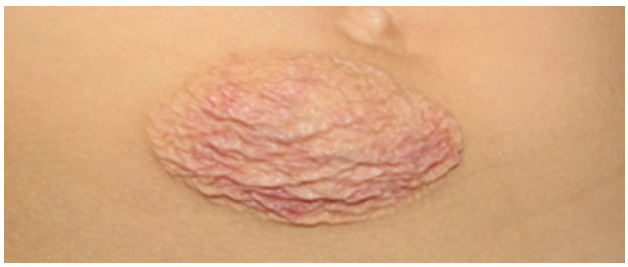

**Fig. 3** Atrophy and fibrofatty residuum of infantile hemangioma

## 1.3 Diagnosis

Diagnosis is made primarily based on clinical characteristics and biologic behavior as already described while histologic diagnosis is currently the gold standard. The histopathologic features of IH vary depending on the stage of the IH life cycle. Initially, rapidly proliferating, plump, endothelial-like cells and pericytes are present. Vascular lumens begin to appear during the early proliferative phase. Later during the proliferating phase, fibrous septae containing large vessels separate lobules of plump endothelial-like cells. Mitotic figures, apoptotic bodies, and mast cells may also be present within the IH. Finally, during the involutional phase, flattening of the endothelial-like cells, reduction in mitotic figures, decrease in vessels, and appearance of fibrofatty tissue are noted [9]. Immunohistochemically, positive staining of endothelial cells in IH tumor specimens with GLUT-1, present at all stages, can differentiate IH from other vascular tumors and malformations [10]. The immunodiagnostic marker, GLUT-1, has been useful in differentiating IH from other vascular anomalies such as congenital hemangiomas, which are present at birth and will not stain with GLUT-1.

Although IHs represent benign tumors, one study found a 24 % complication rate, with 38 % of IH infants receiving therapy [7]. As the authors note, these infants were seen at referral pediatric dermatology centers, most likely overestimating the complication rate and need for treatment found in the study. Complications include ulceration, bleeding, infection, visceral involvement, obstruction of the airway, visual compromise, and disfigurement and can result in a significant amount of morbidity. Management with pharmacologic or surgical treatment is typically reserved for such complicated or problematic IH lesions. Many advances have been made revealing insights into the pathogenesis of the disease, which have potential pharmacologic implications. Herein, we present a review regarding updates on our understanding of the pathogenesis, complications, and current management strategies for problematic IH.

## 2 Pathogenesis

Our understanding of the pathogenesis of IH continues to evolve – albeit many questions remain to be resolved. The tumor is composed of rapidly proliferating, immature, endothelial-like cells building a network of disorganized blood vessels. Dysregulation of both angiogenesis, the development of new vessels from pre-existing ones [11], and vasculogenesis, the de novo formation of blood vessels from endothelial precursors [12], is thought to play a critical role. A variety of factors, both intrinsic and extrinsic [13], are thought to contribute to hemangioma development. Evidence pointing to an intrinsic defect in immature IH cells, leading to aberrant proliferation and differentiation, is provided by in vitro and in vivo experiments involving human IH-derived endothelial cell (HemEC) [14, 15], endothelial progenitor cell (HemEPC) [16, 17], and stem cell (HemSC) populations [18]. Preliminary studies have demonstrated HemEC clonality [14, 15] and HemSC differentiation and recapitulation of human IH after HemSC implantation in nude mice [18]. As such, one hypothesis predicts HemSCs [18] or circulating EPCs [19] to be the cell of origin of IH. Of pharmacologic interest, rapamycin, an inhibitor of the mammalian target of rapamycin (mTOR), was recently shown to block the self-renewal properties of HemSCs, push HemSC differentiation toward a perivascular cell phenotype rather than an adipogenic one, and inhibit blood vessel formation in the murine IH explant model [20].

One initial hypothesis has described a placental embolic origin for hemangiomas. Expression of GLUT-1 along with Fc-γ-receptor II, merosin, and Lewis Y antigen (placenta-associated vascular antigens) in IH tissue lends support to the theory that the placenta is the origin of site for IH [10, 21, 22]. This molecular profile is shared by IH and human placenta and expressed in capillary endothelial and chorionic villus cells, respectively. Observation of other molecular markers such as embryonic stem cell-associated proteins, embryonic hemoglobin ζ, human chorionic gonadotropin (hCG), and human placental lactogen (hPL) within proliferating IH lesions also argues for an early embryonic origin for IH [23]. Specifically, some speculate a placental, chorionic, villous, mesenchymal core cellular origin [23] whereas others had previously hypothesized a placental trophoblastic origin for IH [24].

Taken together, the metastatic niche theory has been considered for IH [25]. The hypothesis predicts that the chorangioma, benign placental tumors, or the placenta secretes factors that prepare sites and recruit cells for IH development.

Hemangiomas have also been hypothesized to develop as a particular response to hypoxia [26]. As proposed by the authors, the development of the tumor perhaps serves as an effort to normalize a hypoxic environment. This is supported by the tumor's distinct characteristics, unique biologic behavior, and various demographic factors.

A genetic contribution to IH development has also been proposed. Although the majority of cases are sporadic, an autosomal dominant pattern has been described [27]. A follow-up family linkage study demonstrated linkage to chromosome 5q31-33 in three families [28]. Subsequent sequencing of candidate genes in the region revealed somatic mutations in genes encoding vascular endothelial growth factor receptors, VEGFR2 (*FLK/KDR*) and VEGFR3 (*FLT4*), in DNA isolated from two IH tissue specimens [15]. Further evidence in support of a genetic component is provided by missense mutations found in genes encoding VEGFR2 and the integrin-like receptor, tumor endothelial marker-8 (TEM8) (*ANTXR1*) [29]. The mutations were shown to result in increased interactions among VEGFR2, TEM8, and β1 integrin proteins and inhibition of integrin activity in expression experiments with HemECs. In this study, a C482R mutation in *VEGFR2* was observed in HemEC and blood genomic DNA in 2/9 and 8/105 individuals with IH, respectively, a statistically significant finding when compared with controls. Normally, VEGF has a higher affinity for VEGFR1 (both soluble and transmembrane forms) in endothelial cells. Binding of VEGF to VEGFR1 reduces VEGFR2 activity, thereby decreasing endothelial cell proliferation. In IH, the opposite is thought to occur as demonstrated by suppressed VEGFR1 and constitutive VEGFR2 expression. Mutated VEGFR2 and TEM8 were shown to decrease nuclear factor of activated T cells (NFAT) activity, which downregulated VEGFR1 expression. Accordingly, an increase in endothelial proliferation results as more VEGF binding to VEGFR2 occurs. Addition of VEGF neutralizing antibodies and soluble VEGFR1 to these experimental cell lines resulted in normalization of constitutive VEGFR2 expression, providing a potential option in future therapeutic development.

## 3 Complications

The majority of IHs are uncomplicated and do not require treatment. However, intervention may be necessary for IHs that are located in life- or function-endangering locations, are disfiguring, and/or result in ulceration. Large size, facial location, and segmental lesions, in particular, are predictors for complications [7].

### 3.1 Ulceration

The most common complication of IH is ulceration (Fig. 4), which can lead to pain, irritability, difficulty

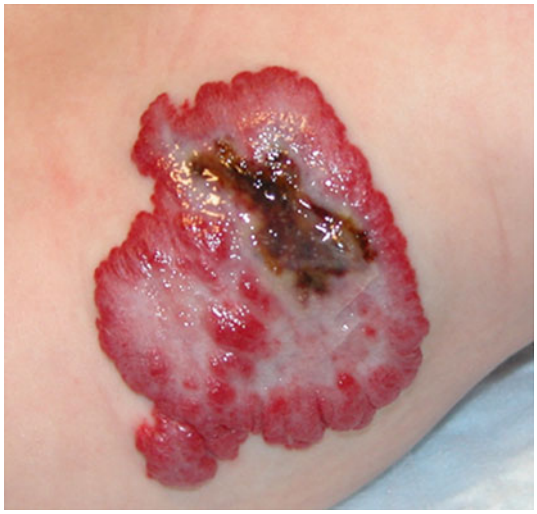

**Fig. 4** Ulcerated superficial infantile hemangioma

feeding and sleeping, infection, bleeding, disfigurement, and permanent scarring. In one prospective study, 173 out of 1,096 children with IH (16 %) developed ulceration in their lesions [30]. Ulceration was noted to be location dependent – mainly found on the lower lip, neck, or anogenital regions, where friction and maceration occur. The study also noted that large, segmental, and mixed IHs were more prone to ulceration. In an additional study, early white discoloration of IH was noted to be an indicator of impeding ulceration [31]. Significant bleeding from ulceration (one that requires blood transfusion) is fortunately rare in IH [30]. Ulcerated tumors can be treated with systemic therapies or other modalities such as pulse dye laser (PDL) [see Sect. 5.7] [32]. Additional methods of pain control may be necessary in the management of ulcerated IH. Proposed reasons for ulceration include an outgrowth of blood supply, rapid expansion beyond the skin's elastic capabilities, and mechanical trauma [30, 33, 34].

### 3.2 Periorbital Infantile Hemangiomas

IHs that are located periorbitally are at risk of visual compromise [35]. The most common complication is astigmatism due to pressure from the IH on the cornea [36]. Amblyopia is significant as block of visual input to the developing striate cortex by the IH can result in permanent blindness [37]. Involvement of the posterior orbit may result in exophthalmos or displacement of the globe. Strabismus, exposure keratopathy, and optic neuropathy are other possible complications of periorbital IH [36]. Evaluation by an ophthalmologist is recommended as measures such as patching of the unaffected eye can play a key role in prevention of complications. Regular follow-up with an ophthalmologist during the proliferative phase of the tumor is also recommended. Imaging (magnetic resonance imaging [MRI] or ultrasound) may be useful in the evaluation of periorbital IHs suspected of having a deeper component or for lesions for which definitive diagnosis is not clear. Pharmacologic and/or surgical therapy may be necessary and is considered on an individual case-by-case basis.

### 3.3 Airway Infantile Hemangiomas

Airway involvement of IHs can result in difficulty breathing and subsequent respiratory failure. Airway hemangiomas typically become symptomatic between 6 and 12 weeks of age; however, they can present earlier or later with cough, stridor, hoarse cry, and/or cyanosis [36, 38, 39]. Close monitoring for the first 6 months in high-risk lesions is recommended. Risk of airway involvement is highest when lesions are segmental and involve the face in a mandibular or 'beard' distribution – a region that encompasses the preauricular region down toward the chin and neck (Fig. 5) [40]. Recent data in support of the mandibular distribution as a risk factor for airway IH come from a case series study of infants with large facial and airway hemangiomas [41]. In the study, 13 of 17 (76 %) infants with airway IH were found to have bilateral mandibular involvement. Furthermore, 27 % of infants (17/64) with facial IH involving the mandibular region had airway IHs. The study also found that 47 % (8/17) of infants with airway and facial IHs were diagnosed with PHACE syndrome (see Sect. 3.5). Two additional facial IH patterns were observed to be associated with airway IH: (1) reticular or telangiectatic IH in a frontotemporal/mandibular distribution and (2) unilateral multisegment, large facial IHs. Of note, airway hemangiomas can occur in children without associated cutaneous lesions. Management by an otolaryngologist and multi-disciplinary team is typically required and medical therapy is usually first-line. Tracheotomy is reserved for emergent and/or resistant cases as the procedure has a high complication and morbidity rate [42].

### 3.4 Visceral Infantile Hemangiomas

Non-cutaneous IHs can occur most often in the gastrointestinal (GI) tract, liver, pancreas, spleen, and CNS and are commonly asymptomatic. However, complications may result, depending on the particular site of involvement, and include GI bleeding, cardiac heart failure, obstructive jaundice, and CNS injury [37, 43, 44]. The presence of multifocal cutaneous hemangiomas is a strong predictor for visceral involvement, although visceral IH can occur in the absence of cutaneous IH. Consequently, evaluation with a liver ultrasound is recommended for children with five or more cutaneous lesions [45, 46].

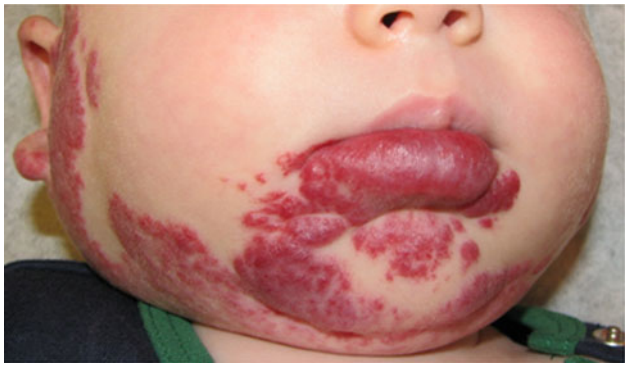

**Fig. 5** Segmental 'beard' or mandibular distribution infantile hemangioma

Recently, an association between facial segmental IHs and GI bleeding was observed in a multicenter, retrospective, case series study [47]. The facial segmental pattern of cutaneous IH associated with GI bleeding in this series was morphologically distinct from the traditionally described multifocal lesions of diffuse neonatal hemangiomatosis, a term used to associate cutaneous and visceral vascular lesions. GI lesions were similarly segmental and found to involve the lower GI tract. Risk factors for GI bleeding and segmental IH of the GI tract noted in the study included female infants with large segmental IH of the head and neck and arterial vasculopathy of the neck, chest, and abdomen and aortic coarctation, respectively.

Albeit rare, large or multifocal hepatic hemangiomas can result in cardiac heart failure due to arteriovenous and portovenous shunting. In such cases, pharmacologic therapy or emergent embolization may be necessary. Large hepatic lesions may also cause abdominal compartment syndrome, respiratory impairment, and hypothyroidism [48]. Hypothyroidism in association with hepatic IH has been reported in various case reports [49–51]. The consumptive hypothyroidism in hepatic IH is thought to occur due to increased inactivation of the T4 and T3 thyroid hormones by D3 iodothyronine deiodinase. Another proposed mechanism hypothesizes that inactivation of the D2 iodothyronine deiodinase, an enzyme that is required for maintaining cytoplasmic T3 levels, by an inhibitor secreted by the tumor contributes to the impairment of intracellular T3 generation, pituitary resistance to T4, and resultant hypothyroidism of hepatic IH [52].

### 3.5 Associated Anomalies and Syndromes

Large, segmental hemangiomas of the head and neck can be associated with a particular set of congenital anomalies, known collectively as PHACE syndrome. PHACE is an acronym for *p*osterior fossa malformations, infantile *h*emangiomas, *a*rterial anomalies of the great cerebral vessels, *c*ardiac defects/coarctation of the aorta, and *e*ye anomalies [53]. Sternal malformations or supraumbilical raphe can also be present as part of the syndrome. The diagnosis of PHACE syndrome is made based on a defined set of major and minor criteria [54]. Of note, patients may or may not have every component of the syndrome. A female predominance exists as in non-PHACE IHs [55]. However, unlike infants with non-PHACE IHs, infants with PHACE syndrome are typically born full term, normal birth weight, and singleton [2]. Pathogenesis is unknown but is believed to be due to a disruption in early embryonic development. Clinically, patients typically present with large, segmental, facial hemangiomas. Cerebrovascular abnormalities are common, which can increase the risk of stroke. In one systematic review of the literature, aplasia, hypoplasia, or occlusion of a major cerebral artery were found to be significant risk factors for arterial ischemic stroke [56]. Structural brain anomalies include Dandy-Walker malformation, cerebellar hypoplasia, and dysgenesis of the vermis, all of which can lead to developmental motor delays. Cardiac anomalies consist of coarctation of the aorta, aortic arch anomalies, and septal defects. Eye anomalies include optic nerve atrophy and retinal vascular abnormalities, among other defects. Sternal malformations (pit, clefting) can also occur. Although rare, endocrine abnormalities such as hypopituitarism, hypothyroidism, growth hormone deficiency, and diabetes insipidus, may be associated with PHACE syndrome. Evaluation of these organ systems is imperative when PHACE syndrome is suspected in infants who present with large segmental IHs. Various modalities such as MRI and magnetic resonance angiogram (MRA) of the head and neck are useful in the work-up and diagnosis of PHACE syndrome.

IHs located in the lumbosacral region (Fig. 6) are at risk of underlying developmental anomalies, particularly spinal dysraphisms. Anorectal and urinary tract defects may also be present. These associations have been variably named with several acronyms (PELVIS, SACRAL, and LUMBAR) [57–59]. Evaluation with MRI is therefore recommended for lumbosacral IH [60].

## 4 Prediction and Treatment Response Measurement

Variations in IH behavior have posed difficulties for clinicians when it comes to predicting severity and subsequent need for treatment. Furthermore, no standardized methods exist to measure IH growth, involution, and therapeutic response [61], making it difficult when attempting to achieve consistency and accuracy when determining outcome in various clinical treatment trials. A variety of methods have been used to predict and measure treatment response. One prospective study including 1,058 children found that large size, facial location, and

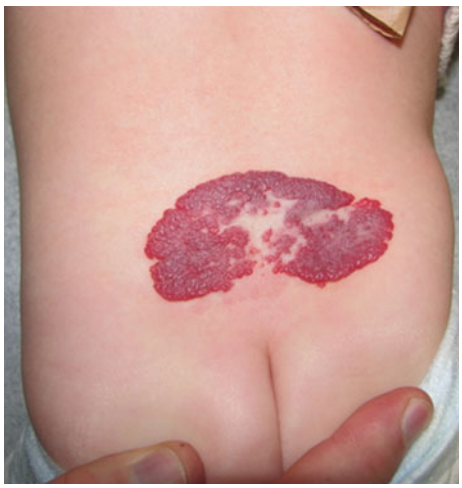

**Fig. 6** Lumbosacral infantile hemangioma

segmental morphology were important predictors of short-term complications [7]. The Hemangioma Severity Scale (HSS) and the Hemangioma Dynamic Complication Scale (HDCS) were recently developed and found to be reliable scales for IH severity and complications [62]. Measurements in IH size using diameter, surface area, volume, and thickness using imaging modalities such as ultrasound have also all been utilized [8, 61, 63–65]. Volumetric parameters are often difficult to assess given some IH tumors' anatomic location, deep components, and variability within the lesion [61]. However, several mathematical techniques modeling IH as half spheres [63, 64] or ellipsoids [61] exist for volumetric evaluation. Additionally, visual analog scales (VAS) allow clinicians to determine IH size, appearance, and color [66] – although this method can be subjective. Other endpoints that have been utilized include softness, number of complications, and measured vascularity.

## 5 Treatment Options

Although no US FDA-approved therapies are available for the treatment of complicated IH, several off-label options do exist. The two mainline therapies were both discovered incidentally, the first, corticosteroids, and the second, propranolol. There are few prospective, randomized, clinical trials using standard treatment and response criteria for the treatment of IH. The variable biologic behavior and tendency for spontaneous involution has made design of stringent clinical trials difficult. Standardized management and treatment protocols have been difficult to establish due to the lack of safety and effectiveness data. In addition, indications for treatment vary and range from life-threatening airway IH to the management of complications such as ulceration and periorbital involvement. Therefore, treatment goals and endpoints differ depending on the indication and site of IH involvement (e.g. volume reduction for periorbital IH vs. reducing time to healing for ulceration). Furthermore, infantile hemangiomas are self-limited tumors and naturally undergo involution. Taken together, careful consideration of the potential risks of adverse effects against the benefits of treatment is undertaken prior to initiation of treatment.

### 5.1 Oral Corticosteroids

Systemic corticosteroids have been used as mainline therapy for hemangiomas since the 1960s [67, 68] when marked improvement of an IH lesion was observed in a patient treated with corticosteroid therapy for thrombocytopenia [67]. Since its incidental discovery, information regarding corticosteroid treatment protocols, efficacy, and safety for IH has mainly derived from anecdotal experience, case reports/series, and retrospective studies. One randomized study conducted from 2002 to 2005 compared daily oral prednisolone (2 mg/kg/day in two divided doses; tapered at 1 mg/month over 6–9 months) with monthly intravenous (IV) pulses of methylprednisolone (30 mg/kg/day infused over 1 h daily for a duration of 3 days) in 20 infants [66, 69, 70]. The investigators found a significant improvement in IH size using the VAS in the oral prednisolone group when compared with the IV methylprednisolone group at 3 months and 1 year of treatment. However, infants in the oral corticosteroid group had a higher risk of developing adverse effects. One systematic literature review of corticosteroid therapy in the treatment of IH determined an 84 % response rate and a 36 % rebound rate with the use of prednisone therapy [71].

Most infants are initiated at a dose of 2–3 mg/kg/day of systemic prednisone and continue therapy for several months. Response to oral corticosteroids may be variable [72]; however, the lesion typically stops proliferating within the first few weeks of treatment [73, 74]. Tapering of corticosteroids is typically recommended as abrupt cessation during the proliferative phase may lead to rebound growth [75].

Adverse effects of systemic corticosteroids are well documented and include cushingoid facies, altered mood, sleep disturbances, agitation, gastric upset, adrenal suppression, immunosuppression, hypertension, and delayed skeletal growth – although catch-up growth typically occurs after therapy discontinuation [76–78]. Therapy with histamine $H_2$ receptor blockers can be used with corticosteroid therapy. The increased risk of infections due to immunosuppression has led some clinicians to consider prophylaxis against *Pneumocystis jirovecii* pneumonia (previously known as *Pneumocystis carinii* pneumonia, or PCP) with trimethoprim-sulfamethoxazole (cotrimoxazole), particularly in children with additional risk factors.

However, the exact incidence of PCP in infants treated with corticosteroids for IH in unknown and PCP prophylaxis is not routinely administered, but may be considered. This consideration is based on two reports of PCP in infants treated with corticosteroids for IH [79] and further substantiated by a prospective study showing decreased levels of T and B lymphocytes in 16 corticosteroid-treated infants with IH [80]. Antibody titers against tetanus and diphtheria were not found to be protective in the study in 11/16 and 3/16 patients, respectively [80]. Thus, it has been suggested that antibody levels be checked and additional immunizations given if titers are not found to be protective in infants who are immunized during concomitant treatment with corticosteroids for IH.

### 5.2 Intralesional and Topical Corticosteroids

Intralesional and topical corticosteroids are traditionally reserved for small, localized IH. Conversely, large or life-threatening IHs are not amenable to intralesional or topical corticosteroid treatment. Multiple injections [35] of intralesional triamcinolone acetonide (10–40 mg/mL) [81, 82] over a period of 2–8 weeks are typically needed and doses should not exceed 3–5 mg/kg/treatment. Furthermore, intralesional treatment of periocular IH should be managed with caution as adverse effects such as central retinal artery occlusion [83], eyelid necrosis [84], skin atrophy, and adrenal suppression [85] have been observed.

The exact mechanism of action of corticosteroids on IH is unknown. Proposed mechanisms of action include promotion of adipocytic differentiation, inhibition of anti-adipogenic factors, and anti-vasculogenesis [18, 86].

### 5.3 Oral β-Blockers

The non-selective β-blocker, propranolol, was introduced as a treatment option for problematic IH in 2008 when marked improvements in IH lesions in two individuals were observed after systemic propranolol was administered for cardiac indications [65]. Numerous case series and small studies have reported on the efficacy of propranolol in the treatment of IH and have described cessation of growth and rapid reductions of tumor volume with treatment [87–96]. Although results from large comparative studies have not yet been published, many clinicians and one retrospective comparative study have noted a faster response of the tumor to propranolol when compared with corticosteroids [97]. Within a few years of its introduction, propranolol has revolutionized the approach to IH management and has quickly become a mainline therapy. However, data from large-scale, randomized controlled trials (RCTs) evaluating the efficacy and safety of propranolol for the treatment of IH are not yet available and standardized management and treatment protocols are not yet developed. A few RCTs, however, are currently underway [69, 70]. Recently, results from one small randomized, double-blinded, placebo-controlled, parallel-group trial were reported [98]. The study randomized 40 children, aged 9 weeks to 5 years, with facial IHs or IHs at sites of potential disfigurement to receive oral propranolol hydrochloride 2 mg/kg/day divided three times daily or placebo for 6 months. Inhibition of IH growth, measured by changes in IH volume, color, and elevation, was noted. No major adverse effects were reported – although one child withdrew from the study due to an upper respiratory tract infection.

The off-label use of propranolol has led to variability in pre-treatment work-up, treatment dosing (initiation, goal, and frequency), duration, and monitoring. Approach to IH treatment is dependent on factors such as age at initiation, history of prematurity, growth characteristics, and location of the hemangioma, among other factors. A multi-disciplinary approach can be considered with consultation of a cardiologist. Dose at initiation typically ranges from 0.5 to 3 mg/kg/day divided two or three times a day. Duration of therapy can vary anywhere between 6 weeks to several months. Setting of initiation also ranges from a 24- to 48-h inpatient admission to outpatient initiation. Baseline hemodynamic parameters including heart rate and blood pressure can be established at initiation 1–3 h after first dose and dose escalation and monitored thereafter. A consensus-derived approach to the initiation and use of oral propranolol for IH was recently published. This document provides a number of recommendations that arose from a review of existing evidence, including when to treat complicated IH; contraindications and pretreatment evaluation protocols; propranolol use in PHACE syndrome; formulation, target dose, and frequency of propranolol; initiation of propranolol in infants; cardiovascular monitoring; ongoing monitoring; and prevention of hypoglycemia [142].

Other methods of pre-treatment evaluation and monitoring have included baseline echocardiography, ECG, and evaluation of at-risk infants for PHACE syndrome. Regarding risk of rebound growth, one case series reported a recurrence rate of 19 % after discontinuation of propranolol therapy, which occurred between 0 and 6 months [99].

Various early trials and reports over the past 40 years have described the use of β-blockers when used in the treatment of hypertension, supraventricular tachycardia, and other cardiac conditions in children [100–102]. Thus far, propranolol appears to have a relatively good safety profile for use in IH infants based on available evidence from case reports/series and small trials [98]. Nevertheless, its safety in the treatment of IH infants, whose heart rates and blood pressure are otherwise within normal range, is

yet to be conclusive. Potential serious adverse effects of propranolol to consider are bradycardia, hypotension, hypoglycemia, bronchospasm, and congestive heart failure. Other adverse effects include neuropsychiatric (changes in sleep, depression, night terrors) and gastrointestinal disturbances (abdominal cramping, nausea, and vomiting). CNS-related adverse effects are attributed to the lipophilic properties of propranolol and high concentrations found in the brain. Reported adverse effects in IH infants treated with propranolol have included hypotension [103], hypoglycemia [103–105], bronchial hyperreactivity [103], hyperkalemia [106], sleep and gastrointestinal disturbances, and cold extremities [103].

Unexpectedly, the most commonly reported, serious adverse effect of propranolol in IH has been hypoglycemia, particularly in the setting of prolonged fasting and illness [103–105]. Theoretically, infants with IH treated with propranolol are at a higher risk of hypoglycemia due to limited glycogen stores and inability to communicate [104]. Furthermore, previous treatment with systemic corticosteroids may also theoretically increase the risk of hypoglycemia due to adrenal suppression and reduction in the counter-regulatory cortisol response. As such, to prevent hypoglycemic episodes, it is recommended that caregivers be educated on the signs and symptoms of hypoglycemia (e.g. drowsiness and rarely seizures) and instructed on proper administration (e.g. always given with feeding and discontinuation with fasting and illness).

One special population of infants with IH to consider includes those with PHACE syndrome. Theoretically, propranolol may decrease cardiac output and increase the risk of stroke in infants with PHACE due to their underlying arterial cerebrovascular, cardiac, and arch anomalies. To date, the use of propranolol in individuals with PHACE syndrome has been described in only a limited number of PHACE cases with no reports of complications [107, 108]. Caution is nonetheless justified when using propranolol in patients with PHACE syndrome due to the risk of cerebral ischemia and stroke.

Another population for special consideration when using propranolol includes infants at risk of high-output cardiac failure. While rare, infants with large or multifocal hepatic hemangiomas can develop high-output cardiac failure due to arteriovenous and portovenous shunting. One theoretical risk to using propranolol in children with liver IH is decompensation of heart failure resulting from decreased ability of the heart (i.e. reduced HR and contractility from β-blockade) to respond to high-output demands. Hepatic IHs have been reported to respond with the use of propranolol [95, 109–113]. Of note, one case described a significant improvement in both the hepatic IH lesions and high-flow cardiac overload (assessed by symptom improvement, pulmonary transvalvular gradient reduction, and echocardiographic features) in a patient treated with first-line propranolol [113]. The authors suggest that propranolol could potentially be used as first-line therapy in infants with hepatic IH despite the presence of cardiac symptoms due to high-flow overload. However, this option would not be available for infants with life-threatening high-output heart failure as emergency embolization may be necessary. Further trials and studies are needed to evaluate the safety of propranolol and other β-blockers in this special population of individuals with IH.

Management with other β-blockers such as acebutolol has been reported in a few cases given its β1 selectivity, reported favorable adverse effect profile over propranolol, and twice-daily dosing [114–116]. Doses ranged from 8 to 10 mg/kg/day. Reported patients received acebutolol for up to 1 year and a few infants were continued on therapy at the time of publication of the cases. Another alternative to propranolol includes atenolol, a hydrophilic β1-selective blocker, which has been hypothesized to produce less CNS and pulmonary adverse effects when compared with propranolol in infants treated for IH [117].

### 5.4 Topical β-Blockers

Given the success of oral propranolol, many practitioners have used topical β-blockers for the treatment of superficial, localized IH. Periocular IHs are especially amendable to the use of this medication. There are currently no commercially available forms of topical propranolol; however, intraocular preparations of β-blockers used for glaucoma exist. As with the other therapies for IH, none of these preparations is approved by the FDA for the treatment of IH. Topical β-blockers such as 0.1 or 0.5 % timolol maleate gel-forming solutions (twice daily) have been applied with promising results [118–120]. Topical propranolol in an oil-based cream or hydrophilic ointment applied twice a day in a thin layer (approximately 1.5 mg/cm$^2$ or 15 μg propranolol/cm$^2$) has also been reported to be effective for superficial IH lesions [121]. Although not specified in the abovenamed studies, we recommend limiting the dose to one to two drops (1 mL) twice daily due to the theoretical risk of transcutaneous absorption. Regarding transcutaneous absorption, comparison studies between topical timolol and propranolol are needed. Systemic absorption in young infants can occur with topical application of timolol. Systemic adverse effects such as bradycardia and bronchial hyperreactivity were observed in 3–4 % of children with pediatric glaucoma when treated with intraocular timolol [122, 123]. Various clinical trials studying the efficacy and safety of topical β-blockers for IH are currently underway [124]. Data from these and subsequent studies will help determine the efficacy and

safety of topical applications of β-blockers in the treatment of IH.

Proposed mechanisms by which β-blockers mediate their effect on IH include decreased expression of vascular endothelial growth factor and basic fibroblast growth factor, induction of apoptosis [125], vasoconstriction [65], and effects on the renin-angiotensin system [126].

### 5.5 Vincristine

Information on vincristine, a vinca alkaloid and chemotherapeutic agent, and its role in IH management mainly derives from a limited number of case reports [127, 128]. Its use in IH has traditionally been reserved for and shown to be effective in the treatment of aggressive and corticosteroid-resistant and/or contraindicated cases. With the advent of the use of propranolol in IH therapy, the need for vincristine as a therapeutic option for IH is decreasing. Vincristine has also been used for other vascular anomalies distinct from IH such as kaposiform hemangioendothelioma and tufted angioma, particularly in the setting of the Kasabach–Merritt phenomenon [36]. No data from clinical trials on the safety and efficacy of vincristine in the treatment of IH have been published. However, results from one ongoing, phase II, randomized clinical trial registered in 2007 are pending (closed recruitment) [69, 70].

Vincristine is administered via a central venous line. Doses for IH have ranged from 0.05 to 1.5 mg/m$^2$. Once-a-week doses have been administered for a total of three to four doses at intervals of 1–3 weeks [128].

Adverse effects of vincristine include neurotoxicity manifested as constipation, abdominal pain, paralytic ileus, jaw pain, peripheral neuropathy, and neuromyopathy (foot drop). These particular adverse effects are usually more marked in adults than in children [128]. Although rare, leukopenia and anemia can also result from vincristine use.

Vincristine is an inhibitor of cell mitosis and microtubule formation. Its anti-angiogenesis properties [129, 130] are thought to play a role in IH growth cessation. The drug is also known to induce apoptosis of tumor and endothelial cells.

### 5.6 Interferon-α

Interferon-α (2a and 2b) therapies have been reported to be effective in several, small case reports for life-endangering IH; however, the potential for irreversible neurotoxicity of interferon-α therapies has severely limited its use in IH [131, 132]. Common yet typically transient adverse effects include fever, irritability, malaise, neutropenia, and liver enzyme abnormalities. Of greatest concern are reports of irreversible cases of spastic diplegia that have occurred in several infants treated with interferon-α for IH [133, 134]. It is thus recommended that infants aged less than 1 year not receive interferon-α and those aged >1 year with life-threatening IH who are resistant to other available therapies should undergo careful neurologic evaluation and monitoring if treatment with interferon-α is pursued [135]. Its mechanism of action in IH has been attributed to its anti-angiogenesis and basic fibroblast growth factor inhibition properties [136].

### 5.7 Pulse Dye Laser

The role of PDL in the treatment of proliferating IHs remains controversial [137] as some studies have shown no effect on IH clearance with PDL [138]. Its depth of penetration of 1.2 mm limits its effects on any deep components of IHs. For the management of ulceration and residual effects of IH, however, PDL is an available option. PDL has been shown to be effective in the treatment of ulcerated hemangiomas, mainly decreasing pain and time to re-epithelialization [32, 139]. Furthermore, PDL is useful in reducing the post-involution effects of IH such as telangiectasias and erythema. Adverse effects of PDL include scarring, skin atrophy, and hypopigmentation, and counter-intuitively, PDL may lead to ulceration itself [138, 140].

### 5.8 Surgery

Excisional surgery is mainly utilized for removal of residual fibrofatty tissue and scars; however, early surgical excision may be used for function-threatening, life-endangering, and/or disfiguring lesions when pharmacologic agents are contraindicated and/or fail [141].

## 6 Conclusion

IHs are intriguing tumors, particularly with regard to their biologic behavior and management of these tumors can be quite challenging. As reviewed, several modalities exist for the treatment of IHs. Currently, the two mainline therapies being used for the treatment of IH include propranolol and corticosteroids, and a combination of both therapies can be considered as a potential therapeutic approach. As no FDA-approved treatment options are available for IH, clinicians often rely on anecdotal experience and case reports from the literature, resulting in variability in management. Various questions remain to be answered and results from large-scale RCTs are eagerly anticipated.

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