Infantile hemangiomas, complications and treatments

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■ Abstract

Infantile hemangiomas (IHs) are the most common vascular tumors of infancy. While the majority regress without the need for intervention, approximately 10%, often site dependent, can cause serious complications and require treatment. IH complications can be categorized as life threatening, obstructive, ulcerative or disfiguring. Life-threatening complications include airway and hepatic IHs. Functional complications obstructing vital structures or impairing function include periocular, nasal, labial, parotid, auricular, and breast IHs. Local complications arise from ulceration or those in cosmetically sensitive areas. Therapeutic options for complicated IHs include pharmacologic (topical or systemic), surgical, or laser interventions. Topical agents are best employed for small, superficial, and localized IHs; while systemic therapy is reserved for larger IHs and those with more aggressive growth characteristics with propranolol as first-line therapy.

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nfantile hemangiomas (IHs) are the most common benign soft-tissue tumors of childhood, with a reported incidence of approximately 5%.[1,2] IH occurs at a higher frequency in female than male infants with an ethnic predilection for Caucasians. Low birth weight appears to be the most significant risk factor, with a 40% increase in risk for every 500-gram decrease in birth weight.[3,4] Prospective studies have also identified prematurity, multiple gestation, increased maternal age, in-vitro fertilization, pre-eclampsia, and placental anomalies as risk factors.[1,5]

Complications

While the majority of IH are uncomplicated and do not require treatment, in approximately 10% of cases, intervention may be necessary. This is true for IHs that are situated in life-threatening locations, result in functional impairment, have visceral involvement, are disfiguring, or result in ulceration.[6] One study of >1,000 children with IH seen in pediatric dermatology practices reported a 24% complication rate with 38% requiring therapy, although the higher numbers may reflect referral bias.[7] The study also found that the strongest predictor for required intervention was segmental subtype (PHACE, LUMBAR/PELVIS), with large size and facial location being other risk factors (Table 1).[7]

Local complications

Ulceration

Secondary ulceration is the most common complication seen in IH, with frequency ranging from 10%-30% (Figure 1, Figure 2).[8] The specific mechanisms causing ulceration are poorly understood; however, it has been hypothesized that rapid expansion of the tumor may cause it to outgrow its blood supply.[9] In a prospective study of 1,096 children with IHs, the majority of ulcerations occurred by 4 months of age during the proliferative growth phase. Ulcerations were more commonly associated with large size, mixed clinical morphologic type, segmental distribution, and lower lip, neck and anogenital location.[9] Another study found that one-third of all ulcerated IHs are found in the diaper region.[10] The potential adverse outcomes from ulceration are multiple, including pain, irritability, diminished feeding and sleeping, secondary infection, scarring, and disfigurement.[9]

The management of ulcerated IH includes local wound care,

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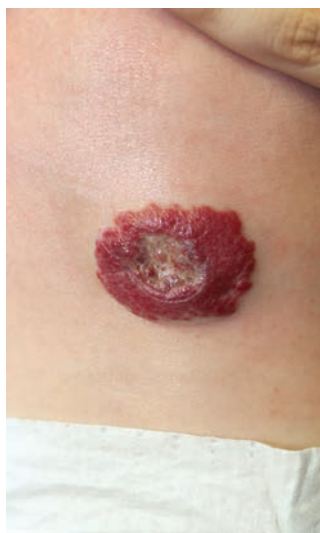[2]School of Medicine, University of California, San Diego; La Jolla.
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■ TABLE 1. Complications arising from infantile hemangioma and indications for treatment

Life-threatening risk	
Airway IH	Respiratory distress
Multiple cutaneous IH	Evaluate for hepatic involvement
Large cutaneous IH	High output congestive heart failure
Large hepatic or parotid IH	Consumptive hypothyroidism
Functional risk	
Periocular IH	Amblyopia
Nasal IH	Cyrano nose deformity
Lip IH	Interference with feeding
Auricular IH	Loss of hearing, cartilaginous deformity, infection
Breast IH	Breast hypoplasia
Ulceration risk	
Perineal IH	Pain, infection, scarring

Abbreviation: IH, infantile hemangioma.

■ **FIGURE 1.** Ulcerated IH in the diaper region with pain and risk of infection

■ **FIGURE 2.** Ulcerated IH on the trunk with pain and concern for scarring

■ **FIGURE 3.** IH in "beard" distribution with associated subglottic hemangioma

pharmacologic therapy, laser, or surgical excision. Early treatment with appropriate wound care is essential to arrest progression of ulceration and to minimize sequelae. Several studies of ulcerated IHs showed that there was no uniformly effective modality, and frequently several treatments were used concurrently.[10,11] The decision to use specific therapies was dependent on the age of the patient, location, size, and stage of the IH. Treatments included topical preparations of timolol, metronidazole and mupirocin, barrier creams, bio-occlusive dressings, systemic antibiotics for infection, oral propranolol, intralesional and systemic corticosteroids, pulsed-dye laser, and surgical excision. Complete wound healing typically occurred following 3 months of therapy regardless of treatment regimen;[10] additionally, pain control with oral and topical analgesics were commonly administered.[10,11] Timolol gel has been reported to successfully treat ulcerated IHs in the perianal region.[12] Topical brimonidine 0.2%/topical timolol 0.5% has also been effectively used in a single case with the authors hypothesizing that synergistic vasoconstriction via alpha-2-agonist and beta-blocker may be more beneficial than single therapy.[13] A series of patients with ulcerated IHs treated with pulsed-dye laser showed a 91% response with an average of two treatments,[14] while combination pulsed-dye laser and timolol gel showed reduced healing time compared with pulsed-dye laser alone.[15] Systemic therapy with propranolol was found to reduce healing time compared with placebo (8.7 vs 22 weeks)[16] and improve pain control.[17]

Potential for life-threatening complications
Airway infantile hemangiomas

IHs affecting the airway may result in life-threatening complications (Figure 3). While symptomatic airway obstruction can occur with or without cutaneous IHs, skin lesions located within the mandibular distribution, especially when bilateral, are a marker for patients at high risk for airway involvement. Orlow et al proposed 5 cutaneous sites in the "beard distribution" as high risk areas: (1) left preauricular area, (2) right preauricular area, (3) chin, (4) lower lip, and (5) anterior neck. This study demonstrated that patients with involvement of ≥4 of these areas had a 63% association with the symptomatic airway IH.[18] Facial segmental IH in a V3 (mandibular or S3) distribution was also associated with airway involvement in 29% of patients. While the most common location for airway IH is the subglottis, the oral cavity, oropharynx, hypopharynx, larynx, and upper trachea can also be affected.[19] Clinicians should be aware of the signs and symptoms of airway IH, which typically present with biphasic stridor or croup-like cry, with onset most commonly between 6 to 12 weeks of age. Referral to a pediatric otolaryngologist is important for airway evaluation and systemic therapy should be started promptly.[19] Management of airway IHs depend on the extent of involvement. Medical and surgical treatment with propranolol, oral and intralesional steroids, chemotherapy agents (vincristine, alpha-interferon), laser, surgical excision, or a combination of these therapies have been used, with tracheostomy now less frequently performed in view of more medical options. A meta-analysis on the effectiveness of propranolol versus other therapies showed superiority of propranolol compared to steroids, CO_2 laser, or vincristine.[20]

Other organ involvement
Multiple cutaneous IHs in children have been identified as a potential marker for hepatic IHs (Figure 4) with recent evidence suggesting that ≥5 cutaneous lesions mandates screening for hepatic involvement.[21] A multicenter prospective study of 151 patients with ≥5 IHs compared to those with <5 showed that 16% of the infants with >5 cutaneous IHs had hepatic IHs identified on abdominal ultrasound, versus none of

■ **FIGURE 4.** Multiple cutaneous IH with associated hepatic hemangioma

the infants with <5 IHs.[22] A recent study did not show evidence of an increased risk for hepatic IH with large or segmental IH.[23]

Routine screening for hepatic IH in patients with >5 cutaneous IHs showed improved clinical outcomes, with a younger age of diagnosis and a lower incidence of potential serious complications including congestive heart failure, hypothyroidism and mortality compared with those who were not screened.[24]

Propranolol is now the most commonly used therapy for treatment of complicated hepatic hemangiomas.[25,26] Other therapies used pior to propranolol included oral corticosteroids most commonly, with α-interferon, vincristine, actinomycin D, cyclophosphamide, and surgical management considered for refractory cases.

Functional complications
The face is the most common area affected by IHs, with one prospective study reporting involvement in 41% of cases.[27] IHs responsible for functional consequences are mostly located in the periorificial areas.

Periocular infantile hemangiomas
IHs involve the periocular region in 12%-24% of cases[28,29] and can be categorized by location of involvement: (1) eyelid; (2) extra-

conal, behind the bony orbit, outside the extraocular muscles; or (3) intraconal, within the cone of the extraocular muscles (Figure 5; Figure 6; Figure 7). Periocular IHs can permanently affect vision by causing amblyopia (decreased vision due to abnormal visual development) most commonly through direct pressure on the globe inducing astigmatism or myopia, or less frequently through occlusion of the visual axis or induction of strabismus due to mass effect. Mixed and deep IHs that cause exophthalmos can result in exposure keratopathy and tear duct obstruction. IHs involving the upper eyelid location, size greater than one centimeter, ptosis, proptosis, globe displacement, strabismus, and occlusion are all associated with worsened visual outcomes.[30]

If the potential for or actual visual compromise is suspected, the patient should be referred to a pediatric ophthalmologist for further evaluation and, if indicated, imaging with MRI. Given the potential serious consequences of visual compromise, aggressive treatment may be warranted. A review of the use of propranolol for periorbital and orbital IHs showed improvement or complete resolution of IHs in 96% of the cases.[31] Timolol has been used to successfully treat superficial eyelid IHs[32] and several cases have also reported success in the treatment of mixed or deep periorbital IHs with higher timolol dosing.[33,34]

Nasal tip infantile hemangiomas
Nasal tip IH may cause splaying of the alar cartilage during the proliferative phase, resulting in a bulbous or "Cyrano" nose deformity and poor cosmetic outcome (Figure 8).[8] Early intervention with propranolol is often warranted and may avoid the long-term sequelae of nasal deformity and obviate the need for surgery.[35] In cases where the deformity persists, surgical debulking and reconstruction should be considered.[35,36]
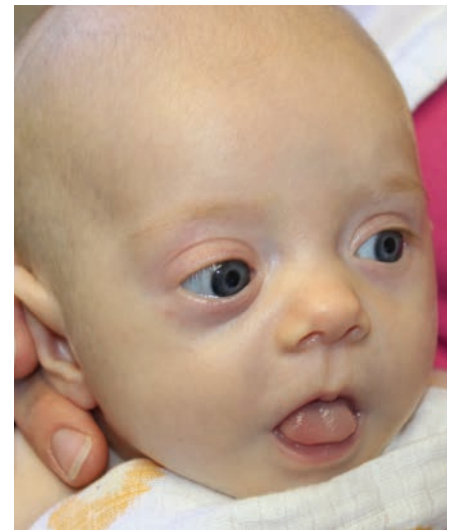
Labial/Lip infantile hemangiomas
Lip IH may influence function or cause disfigurement based on location and size of the lesion (Figure 9, Figure 10). A retrospective study of 342 patients with lip IHs showed that ulceration and scarring were the most common complications affecting 38% of patients,

■ **FIGURE 5.** Upper eyelid IH causing visual impairment and risk of astigmatism

■ **FIGURE 6.** Periocular IH causing upper eyelid ptosis

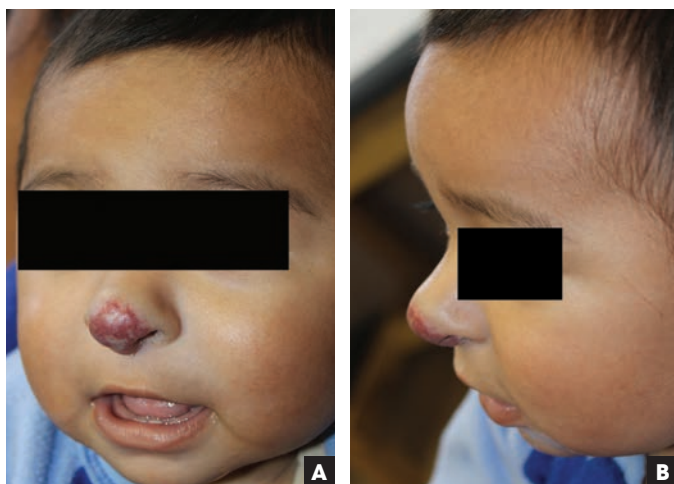■ **FIGURE 7.** Deep periocular IH causing proptosis of the eye

■ **FIGURE 8.** Nasal tip IH causing cosmetic disfigurement **(A)** (front view) **(B)** Nasal tip IH causing cosmetic disfigurement (side view)

with a greater association with segmental distribution and focal lower lip location. Segmental lip IHs, particularly in the mandibular region, should also raise concern for airway involvement.[37] Lip IHs may also interfere with feeding and the development of underlying maxillary and dental structures.[38] While treatment with propranolol should be started early to minimize functional and aesthetic deformity, pulsed-dye laser and surgical reconstruction to define normal anatomic boundaries may also be required following involution.[37]

Parotid infantile hemangiomas

Parotid IH may be part of a segmental cutaneous IH in the maxillary distribution, or isolated to the parotid gland (Figure 11). While the majority of parotid IHs are unilateral, approximately one quarter are bilateral.[39] Compared with IHs in other locations, parotid IHs typically exhibit a longer proliferative growth phase past one year of age, and may require a longer length of therapy.[40] Large parotid IHs can cause deformity of adjacent structures, most commonly ear and lip, and narrowing of the external auditory canal causing conductive hearing loss. Parotid IHs have been associated

■ **FIGURE 9. (A)** Lower lip IH causing feeding difficulties (front view) **(B)** Lower lip IH causing feeding difficulties (side view)

■ **FIGURE 10. (A)** Upper lip IH crossing vermilion border causing cosmetic disfigurement (front view) **(B)** Upper lip IH crossing vermilion border causing cosmetic disfigurement (side view)

with subglottic hemangiomas, and less commonly consumptive hypothyroidism and shunting leading to cardiac failure.[39,41]

Auricular infantile hemangiomas

IHs that involve the ear can cause cartilaginous destruction, cosmetic deformation, diminished auditory input and potential for infection in cases of ulceration (Figure 12, Figure 13). Concerning lesions should be medically managed with propranolol or corticosteroids, with surgical excision recommended as a secondary therapeutic option in complicated cases or for large IHs that are expected to result in permanent deformities if allowed to follow their natural course.[42]

Breast infantile hemangiomas

Large breast IHs, especially those involving the nipple and areola can impair function of the mammary glands and cause breast hypoplasia (Figure 14). A report of a teenage girl with an untreated mixed IH of the breast resulted in pronounced breast hypoplasia noted in puberty. Therefore, mixed or deep IHs involving the breast should be offered systemic therapy to minimize the effect on mammary gland bud development.[43]

Aesthetic Risk

Patients with IHs in cosmetically sensitive areas should be considered for treatment to minimize potential subsequent cosmetic deformity resulting from telangiectasias, fibrofatty residua or atrophic scarring post-involution (Figure 15, Figure 16). The emotional and psychological sequelae resulting from disfiguring IHs may be borne by both the family of the patient and the children themselves as they reach school age and begin to socialize with their peers. It is important for physicians to be aware of these potential issues, and to be involved in counseling families on therapeutic options.[44,45]

Treatment

The majority of IHs are small and regress spontaneously without any need for intervention. However, approximately 10 % of IHs, often site dependent, can cause serious complications and require

■ **FIGURE 11.** Parotid IH with ulceration

■ **FIGURE 13.** Auricular IH with permanent cartilaginous destruction and distortion of the ear

treatment (Table 2).[6] Therapeutic options include pharmacologic (topical or systemic), surgical, or laser interventions. Surgical or laser therapy is usually a second-line choice, and initial treatment frequently utilizes either topical or systemic therapy. In general, topical/local agents are best employed for small, superficial, and localized IHs and/or during early proliferation when there is a possibility local therapy can halt growth. Systemic therapy is reserved for larger IHs—those with more aggressive growth characteristics or high threat of functional impairment—or those not responding to local measures.[46]

Systemic Therapies
Propranolol
Propranolol is a nonselective beta-adrenergic receptor blocker that has a long history of use in pediatric cardiac disease for treatment of hypertension, hypertrophic cardiomyopathy and other cardiac conditions at doses of up to 6-8mg/kg/day.[6] Since the serendipitous discovery of the benefit of propranolol for IHs in 2008,[47] this medication has been rapidly adopted as the first-line treatment for complicated IH lesions, replacing oral corticosteroids. In 2014, Hemangeol (propranolol hydrochloride, Pierre Fabre, Parsippany, NJ) was United States Food and Drug Administration approved and is, as of the publication of this review, the only FDA-approved

treatment for proliferating IHs requiring systemic therapy. To date, there have been 3 randomized controlled trials that have investigated the efficacy of propranolol in IHs.[48-50] The largest trial involved 456 patients comparing a dose of 3mg/kg/day with 1mg/kg/day with placebo for 3 or 6 months, and reported the highest efficacy in the treatment arm receiving 3mg/kg/day for 6 months.[48] In a meta-analysis of 1,264 cases evaluating the efficacy of propranolol for IHs, the response rate of oral propranolol at a mean dose of 2.1 mg/kg/day (range, 1-4mg/kg/day) was 98% (range, 82%-100%).[51] A recent European taskforce survey for use of propranolol in IH scomprising 1,097 patients showed that the majority (85.8%) of practitioners used a maintenance dose of 2mg/kg/day with 91.4% patients showing good or excellent response to treatment. The study also reported no significant differences in treatment response among dosing regimens of <2mg/kg, 2mg/kg and >2mg/kg; however, adverse events were significantly higher in those receiving >2mg/kg.[52] The most common adverse effects were mild and reversible, and included changes in sleep (11%), acrocyanosis (5%) and gastrointestinal symptoms (3%), with serious adverse events of symptomatic hypotension, hypoglycemia and bradycardia infrequently reported.[51]

While consensus guidelines for the use of propranolol for IHs have recently been published in America and Europe,[6,53] there con-

■ **FIGURE 12.** Auricular IH with deformation of the pinna

■ **FIGURE 14.** Breast IH with destruction of normal breast anatomy and risk for breast hypoplasia

■ FIGURE 15. Cosmetically disfiguring IH on cheek with ulceration and potential for significant scarring in cosmetically important area

■ FIGURE 16. Cosmetically disfiguring IH on forehead with risk of protuberant fibrofatty scarring

tinues to be variation amongst practitioners with regards to initiation, maintenance and monitoring of patients while on propranolol. This was supported by a recent survey sent to members of the Society of Pediatric Dermatology, with 75% of respondents reporting that they did not follow consensus guidelines exactly.[54] As initiation and dosing protocols for propranolol seem to vary widely, so does the duration of treatment. This is in part due to the fact that rebound growth has often been noted after discontinuing medication, ranging from 14%-17% in several studies.[51,52] In a recent retrospective study of 997 children, an overall rebound rate of 25% was noted, requiring modification of systemic therapy in 15%. Predictors for rebound growth included age of discontinuation, deep IH component, and female gender. A higher rate of rebound (odds ratio [OR], 2.4) was noted in those treated for less than 9 months compared to those treated for 12 to 15 months.[55] Therefore, many clinicians feel most comfortable maintaining treatment with propranolol until well after the growth phase is completed, which can be up to one year of age.[8] As more information is reported, these recommendations are likely to evolve over time.

Oral corticosteroids

Prior to the widespread use of propranolol, systemic corticosteroids were considered the gold standard for the treatment of proliferating IHs with prednisone and prednisolone at doses of 2 to 5mg/kg/day most commonly reported.[56,57] One meta-analysis showed that 3 mg/kg/day is likely the most effective dose, with an overall response rate of 84%. Higher dosing resulted in greater side effects and lower dosing resulted in fewer responders and greater rates of rebound of up to 40%.[58] Adverse effects were reported in 35% of patients and included cushingoid facies, insomnia, irritability, gastroesophageal reflux, transient growth retardation, and more serious but rare complications of hypertension, osteoporosis, obstructive hypertrophic cardiomyopathy and adrenal insufficiency. Retrospective studies comparing propranolol and prednisone treatment for IHs showed that propranolol induced more rapid and greater clinical improvement, demonstrated better tolerance, and resulted in the need for fewer surgical interventions.[59,60]

Intralesional corticosteroids

Intralesional steroid injections may be effective for small proliferating IHs, particularly of the lip or nasal tip, and may stabilize growth and decrease size of IHs, thus preventing the need for systemic therapy or surgical intervention. While there is no consensus regarding the type of intralesional corticosteroid, optimal dose, or interval between injections, commonly triamcinolone 10mg/mL is administered with doses not exceeding 3mg/kg per treatment session, with 4-6 week intervals between treatments. When dosed appropriately, systemic side effects can be minimized, although the risk of skin atrophy at injection site should be considered.[46,61]

Other cardiovascular therapies

More recently, systemic cardiovascular medications other than propranolol have been under investigation for the treatment of IHs. Nadolol is a nonselective beta-blocker that differs from propranolol in its inability to cross the blood brain barrier, theoretically decreasing adverse events such as sleep disturbances and concerns for memory loss with long-term use. A small study comparing nadolol to propranolol found a similar side effect profile, with nadolol showing greater involution of tumor compared with propranolol.[62] In a study where patients experienced night terrors while on propranolol and were switched to nadolol, authors found that 71% (5/7) of patients had symptom resolution.[63] Atenolol is a cardioselective beta-blocker that principally acts on β1 receptors and may be safer for patients with bronchoconstriction. A small randomized study comparing propranolol to atenolol found similar efficacy and side effect profile, and atenolol has been suggested as a treatment alternative for patients unable to tolerate propranolol because of respiratory contraindications.[64] Captopril, an angiotensin-converting enzyme (ACE) inhibitor, has recently been trialed for treatment of IH, however it was shown to be significantly less efficacious and had higher rates of cardiovascular side effects compared with propranolol.[65]

Historic systemic therapies

Prior to the use of propranolol, patients refractory to glucocorti-

■ **TABLE 2.** Treatment options for infantile hemangiomas

	Indication	Dose	Adverse effects
Local therapy			
Timolol maleate 0.05% gel-forming solution	Superficial localized IH Ulcerated IH	• 1-2 drops BID • In combination with propranolol	Theoretically with same side effects as propranolol
Barrier creams: zinc oxide, petroleum jelly	Ulcerated IH	BID or with every diaper change if in anogenital region	
Topical antibiotics: metronidazole gel, mupirocin ointment	Ulcerated IH	BID	
Systemic therapy			
Propranolol hydrochloride	Complicated proliferating IH	1-3 mg/kg/day divided BID or TID	• Common: acrocyanosis, sleep disturbances, gastrointestinal disturbances • Rare: hypotension, bradycardia, hypoglycemia, bronchospasm
Other therapeutic modalities			
Intralesional kenalog	Mixed/deep small focal IH	10mg/mL, <3 mg/kg/session, every 4-6 weeks	Skin atrophy, telangiectasias
Oral corticosteroids: prednisolone, prednisone	Complicated proliferating IH failing propranolol or with contraindications for use of propranolol	2-5 mg/kg/day	• Common: cushingoid facies, insomnia, irritability, gastroesophageal reflux, transient growth retardation • Rare: hypertension, osteoporosis, hypertrophic cardiomyopathy, adrenal insufficiency
Nadolol	Patients unable to tolerate propranolol due to sleep disturbances		Same as propranolol; does not cross blood brain barrier
Atenolol	Patients with contraindications for propranolol due to bronchoconstrictive conditions		Same as propranolol; does not cross blood brain barrier, theoretically no bronchoconstrictive risk
Surgical therapy			
Pulsed-dye laser	• Ulcerated IH • Post-involution IH with residual telangiectasias		
Surgical excision	• IH not responsive to propranolol obstructing vital organs • Pedunculated IH • Post-involution IH with cosmetic disfigurement		

Abbreviations: BID, two times a day; IH, infantile hemangioma; TID, three times a day.

coid therapy who had life threatening IHs were treated with interferon-alpha or vincristine with variable efficacy. These therapies have since fallen out of favor due to safety concerns as well as the existence of more effective therapies.

Combination oral propranolol and topical timolol
A recent study exploring the efficacy and safety of oral propranolol combined with topical timolol for mixed IHs showed that combination therapy was both efficacious and well-tolerated, although patients with ulcerated or mucosal IHs were excluded from the study population.[66] This combination requires further investigation with regards to efficacy and safety, particularly given recent findings that timolol is systemically absorbed.[67] Nonetheless, a recent

survey reported 66% of practitioners were using combination topical timolol and oral propranolol to treat IHs in their practices.[54]

Topical/Local Therapies
Topical timolol
Topical timolol was first reported for the treatment of IHs in 2010 and has been shown to be safe and effective for arresting the growth and reducing the size of superficial, small IHs. A randomized control trial of timolol 0.5% gel vs placebo showed that the treated group had greater reduction in size and color. Compared with oral propranolol, there appears to be a slower therapeutic onset of action observed after 12 to 16 weeks of therapy.[68] Other reports have shown a more rapid response within 2-4 weeks,

Prospective study of infantile hemangiomas: demographic, prenatal, and perinatal characteristics. *J Pediatr.* 2007;150(3):291-294.

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