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Title: Clinical Practice Guideline for the Management of Infantile Hemangiomas	

Introduction

Infantile hemangiomas IHs occur in approximately 4% to 5% of infants, making them the most common benign tumor of childhood.

Most IHs are small, innocuous, self-resolving, and require no treatment. However, because of their size or location, a significant minority of IHs are potentially problematic.

They are more common in girls, twins, infants born preterm or with low birth weight (up to 30% of infants born weighing <1 kg are affected), and white neonates. The pathogenesis of IHs has yet to be fully defined. A leading hypothesis is that circulating endothelial progenitor cells migrate to locations in which conditions (eg, hypoxia and developmental field disturbances) are favorable for growth.

Knowledge about IHs has advanced dramatically in the past decade, particularly regarding the unique timing and nature of proliferation and involution, risks of sequel, and newer treatment options. As a result, pediatric providers have an opportunity to improve care and reduce morbidity in infants with IHs by promptly recognizing which IHs are potentially high risk and when intervention is needed.

In the broadest sense, the goal of this CPG is to enhance primary care providers, ability to confidently evaluate, triage, and manage IHs, employing an evidence-based approach.

Specifically, the CPG will:

- Provide an approach to risk stratification and recognition of potentially problematic His.
- Emphasize that early and frequent monitoring in the first few weeks and months of life is crucial in identifying those IHs that require intervention because IHs may change rapidly during this period.
- Review the role of imaging in patients who have His.
- Offer evidence-based guidance for the management of IHs, including indications for consultation, referral and possible intervention, pharmacologic options for therapy, the role of surgical modalities, and ongoing management and monitoring (including parent education).

Highlights of This CPG

- IH growth characteristics are different than once taught.
    - Most rapid IH growth occurs between 1 and 3 months of age.
    - Although IHs involute, this process may be incomplete, leaving permanent skin changes that may be life altering. This is especially true for IHs that are thick.
    - There is a window of opportunity to treat problematic IHs. Consult early (by 1 month of age) for lesions that are potentially high risk because of the following associations:
        - Potential for disfigurement (the most common reason treatment is needed).
        - Life-threatening complications.
        - Functional impairment.
        - Ulceration.
        - Underlying abnormalities.
- Oral propranolol is the treatment of choice for problematic IHs that require systemic therapy.
- Topical Timolol may be used to treat some thin and/or superficial IHs.
- Surgery and/or laser treatment are most useful for the treatment of residual skin changes after involution. They may be used earlier to treat selected IHs.

Definitions:

Hemangioma specialist:

Unlike many diseases, management of IHs is not limited to 1 medical or surgical specialty. A hemangioma specialist may have expertise in dermatology, hematology oncology, pediatrics, facial plastic and reconstructive surgery, ophthalmology, otolaryngology, pediatric surgery, and/or plastic surgery, and his or her practice is often focused primarily or exclusively on the pediatric age group.

Hemangioma specialists should:

• Understand the time-sensitive nature of IHs during the growth phase and be able to accommodate requests for urgent evaluation.

• Have experience with accurate risk stratification and potential complications associated with His.

• Be able to provide recommendations for various management options, including observation, medical therapies, and surgical or laser procedures, and provide counseling regarding the potential risks and benefits of these interventions for specific patients.

• have a thorough knowledge of past and emerging medical literature regarding IHs.

• Such specialists often have 1 or more of the following characteristics:

◦ Participated in a vascular anomalies program during previous medical training.

◦ Devotes a significant part of his or her clinical practice to His.

◦ Is a member of or collaborates with a multidisciplinary vascular anomalies center.

- Maintains membership in professional organizations or groups with a special interest in His.
- Participates in research studies in the field of His.
- Publishes medical literature in the field of IHs.

IHs: infantile hemangiomas:

Benign vascular tumors of infancy and childhood with unique clinical and histopathologic characteristics that distinguish them from other vascular tumors (eg, congenital hemangiomas) or malformations. These characteristics include development during the first weeks or months of life, a typical natural history of rapid growth followed by gradual involution, and immunohistochemical staining of biopsy specimens with erythrocyte-type glucose transporter protein and other unique markers do not present on other benign vascular tumors. Many other entities are also called hemangiomas. Some are true vascular tumors, and others are vascular malformations. Therefore, it is important to use the adjective "infantile" when referring to true IHs.

IHs are classified based on soft-tissue depth and the pattern of anatomic involvement.

Soft-tissue depth:

- Superficial: red with little or no evidence of a subcutaneous component (formerly called strawberry" hemangiomas).
- Deep: blue and located below the skin surface (formerly called "cavernous" hemangiomas).
- Combined (mixed): both superficial and deep components are present.

Anatomic appearance:

- Localized: well-defined focal lesions (appearing to arise from a central point).
- Segmental: IH involving an anatomic region that is often plaque-like and often measuring at >5 cm in diameter.
- Indeterminate (undetermined): neither clearly localized or segmental (often called partial segmental).
- Multifocal: multiple discrete IHs at disparate sites.

In Managing IH, Recommendations for Clinicians

1. **Risk stratification**

   1A. Classify an IH as high risk if there is evidence of or potential for the following:
   (1) life-threatening complications.
   (2) functional impairment or ulceration.
   (3) structural anomalies (eg, in PHACE syndrome or LUMBAR syndrome).
   (4) permanent disfigurement.

   1B. After identifying an IH as high risk, facilitate evaluation by a hemangioma specialist as soon possible.

2. **Imaging**

   2A. Do not perform imaging unless the diagnosis of IH is uncertain, there are ≥5 cutaneous IHs, or associated anatomic abnormalities are suspected.

   2B. Perform ultrasonography as the initial imaging modality when the diagnosis of IH is uncertain.

   2C. Perform MRI when concerned about associated structural

abnormalities (eg, PHACE syndrome or LUMBAR syndrome) .

3. **Pharmacotherapy**

3A. Use oral propranolol as the first-line agent for IHs requiring systemic treatment.

3B. Dose propranolol between 2 and 3 mg/kg per d unless there are comorbidities (eg, PHACE syndrome) or adverse effects (eg, sleep disturbance) that necessitate a lower dose.

3C. Counsel that propranolol be administered with or after feeding and that doses be held at times of diminished oral intake or vomiting to reduce the risk of hypoglycemia.

3D. Evaluate patients for and educate caregivers about potential adverse effects of propranolol, including sleep disturbances, bronchial irritation, and clinically symptomatic bradycardia and hypotension.

3E. May prescribe oral prednisolone or prednisone to treat IHs if there are contraindications or an inadequate response to oral propranolol.

3F. May recommend intralesional injection of triamcinolone and/or betamethasone to treat focal, bulky IHs during proliferation or in certain critical anatomic locations (eg, the lip)

3G. May prescribe topical Timolol maleate as a therapy for thin and/or superficial IHs.

4. **Surgical management**

May recommend surgery and laser therapy as treatment options in managing selected His

5. **Parent education**

Educate caregivers of infants with an IH about the condition, including the expected natural history and its potential for causing complications or disfigurement.

Given the wide variation in IH location, size, and age at presentation, the subcommittee acknowledges that there may be situations in which an IH meets high-risk criteria and, therefore, merits consultation or referral, but the practitioner and parents do not believe this is necessary or practical. Clinical judgment is always involved in such decisions, and any plan of action needs to be individualized based on a number of factors, including location of the lesion, age of child, family preferences, and geographic access to care.

1. **Risk Stratification, Triage, and Referral:**

1A. Classify an IH as high risk if there is evidence of or potential for the following:
(1) life-threatening complications,
(2) functional impairment or ulceration,
(3) structural anomalies (eg, in PHACE syndrome or LUMBAR syndrome), or
(4) permanent disfigurement.

1B. After identifying an IH as high risk, facilitate evaluation by a hemangioma specialist as soon possible.

Key Action Statement 1A. Clinicians should classify an IH as high risk (consideration of early treatment or need for further evaluation) if there is evidence of or potential for the following:

1. life-threatening complications.
2. functional impairment or risk thereof.
3. ulceration or risk thereof.
4. evaluation to identify important associated structural anomalies.
5. risk of leaving permanent scarring or distortion of anatomic landmarks.

1. Life-threatening Complications:

Life-threatening lesions include:

- **Obstructing IHs of the airway:**

Typically involve the subglottis, further compromising the narrowest portion of the pediatric airway. Although the mean age at the time of diagnosis is about 4 months, symptoms usually present much earlier but are often mistaken as infectious or inflammatory croup or reactive airway disease.

Most children who are affected develop 6 biphasic stridor and barky cough as the IH enlarges. Approximately half of infants in whom an airway IH is diagnosed also will have a cutaneous IH. Segmental IH of the lower face ("beard distribution") or anterior neck and oral and/or pharyngeal mucosal IHs are the greatest risk factors for an airway IH.

- **Liver IHs associated with high-output congestive heart failure, and severe hypothyroidism**:

Hepatic hemangiomas have been characterized as occurring in 3 patterns: focal, multifocal, and diffuse; the latter 2 are attributable to IHs, whereas focal lesions more often represent congenital hemangiomas.

Most multifocal hepatic IHs are asymptomatic and do not require treatment. However, a minority of these lesions is associated with macrovascular shunting, causing high flow that can, in rare cases, result in high-output cardiac failure.

So-called "diffuse" hepatic IHs are another rare subset that confers an even greater risk for morbidity and mortality.

Infants who are affected typically present before 4 months of age with severe hepatomegaly, which can lead to potentially lethal abdominal compartment syndrome attributable to compromised ventilation, renal failure attributable to renal vein compression, or compromised inferior vena cava blood flow to the heart.

A consumptive form of hypothyroidism caused by the inactivation of thyroid hormones by type 3 iodothyronine deiodinase present in IH tissue can also be a complication of multifocal or diffuse hepatic IHs. Although liver IHs can occasionally be seen in infants with 1 or no IH of the skin, the greatest risk for liver IHs is in infants who have 5 or more cutaneous IHs, 10 for whom screening ultrasonography is recommended.

Other sites of extracutaneous hemangiomas can occur, including the gastrointestinal tract, brain, and other organs. However, such involvement is rare and occurs mostly in association with large segmental IHs, and screening for these extracutaneous hemangiomas is not recommended unless signs or symptoms are present.

- **Profuse bleeding from an ulcerated IH:**

Severe bleeding, although often feared by parents, is an extremely rare complication of ulcerated IHs. Another potentially life-threatening complication is severe coarctation of the aorta not attributable to IHs but rather to structural anomalies seen in association with IHs in PHACE syndrome.

2. **Functional Impairment:**

Examples of functional impairment include visual disturbance and interference with feeding because of IH involvement of the lips or mouth.

IHs occurring in the periocular region have the potential to cause mechanical ptosis, strabismus, anisometropia, or astigmatism, which can quickly lead to the development of amblyopia.

Specific characteristics that place an infant at a higher risk for amblyopia include an IH size of >1 cm, upper eyelid involvement, associated ptosis, eyelid margin changes, medial location, and segmental morphology or displacement of the globe.

Feeding impairment can occur in infants with IHs involving either the perioral region or the airway. Infants with ulcerated lip IHs may have feeding difficulties secondary to severe pain.

Airway IHs may complicate breathing and swallowing, leading also to impaired feeding.

3. **Ulceration:**

Skin or mucosal ulceration of the IH surface occurs with an estimated incidence of 5% to 21% in referral populations.

Ulceration can lead to significant pain, bleeding, and secondary infection and virtually always results in scarring.

Depending on the anatomic site of involvement, it can result in disfigurement.

Ulceration occurs most frequently in infants younger than 4 months, during the period of active IH proliferation.

Certain types of IHs are at higher risk, including superficial and mixed types, segmental IHs, and those involving the scalp, neck, and perioral, perineal, perianal, and intertriginous sites, the latter likely caused by maceration and friction.

In addition, protuberant IHs can ulcerate as a result of trauma.

Although concern for potential bleeding in IHs is common among caregivers and providers, most IH bleeding is minor and easily controllable with pressure. In rare cases, particularly IHs involving the scalp or with deep ulceration, bleeding can be more profuse, even life threatening.

4. **Associated Structural Anomalies:**

A small subset of children with IHs have associated congenital anomalies.

The best-known phenomenon is PHACE syndrome.

The acronym “PHACES” is sometimes used instead to include potential ventral midline defects, specifically sternal cleft and/or supraumbilical raphe.

Cerebrovascular anomalies, present in more than 90% of patients with PHACE syndrome, are the most common extracutaneous feature of the syndrome, followed by cardiac anomalies (67%) and structural brain anomalies (52%).

The hallmark of PHACE syndrome is a large (often >5 cm in diameter) segmental IH that typically involves the face, scalp, and/ or neck, although in rare cases, the face or scalp are spared, with a segmental IH located on the torso and upper extremity instead.

The risk of PHACE syndrome in an infant presenting with a large segmental IH of the head or neck is approximately 30%. Revised consensus criteria for the diagnosis of PHACE syndrome and the care of infants who are affected have recently been published.

LUMBAR syndrome may best be viewed as the "lower half of the body" equivalent of PHACE syndrome.

IHs in LUMBAR syndrome are almost invariably segmental, involving the lumbosacral or perineal skin and often extending onto 1 leg.

Many IHs in LUMBAR syndrome are minimally proliferative morphologically, with telangiectatic vascular stains predominating over bulkier superficial hemangiomas. In such cases, ulceration can be an early clue to the diagnosis.

Rarely, undergrowth or overgrowth of an affected limb may be present. Like PHACE syndrome, the cutaneous IH and underlying anomalies in LUMBAR syndrome reveal regional correlation. Myelopathy, particularly spinal dysraphism, is the most common extracutaneous anomaly.

5. Disfigurement:

IHs can lead to permanent disfigurement either via scarring of the skin or distortion of anatomic landmarks. The risk of disfigurement is much higher than the risk of functional or life-threatening consequences. The majority of infants who receive treatment of IHs do so to prevent uncontrolled growth leading to permanent disfigurement.

This indication for treatment represents a paradigm shift from the hands-off approach of the late 1950s through 1980s, when many experts recommended treatment only for those IHs causing functional impairment.

One reason for this change is an increased recognition that although IHs involute, they often leave behind permanent skin changes that, although not life or function threatening, are potentially life altering.

Moreover, with the advent of β-blocker therapies for IHs, there are now better treatment options with greater efficacy and lower potential toxicity than oral corticosteroids, the previous gold standard. There is also increased recognition that parental and patient quality of life can be adversely affected by visible birthmarks and resultant scarring, particularly in areas that cannot be easily covered with clothing, such as the face, neck, arms, and hands, as well as other emotionally sensitive areas, such as the breasts and genitalia.

The precise risk of a patient in a primary care setting having permanent skin changes from an IH is not known, but in a referral setting, such changes are seen in 55% to 69% of those with untreated His. This risk is greatest in IHs with a prominent and thick superficial (strawberry) component, especially when there is a steep step-off (ie, ledge effect) from affected to surrounding normal skin. However, the degree of superficial thickening may be difficult to predict in early infancy. Thus, even in IHs that do not initially appear to be high risk, it is prudent to serially follow lesion growth and establish a means for prompt evaluation if ongoing or rapid growth is observed because this could alter management.

High-Risk IHs:

IH Clinical Findings	IH Risk
Life-threatening :	
"Beard-area"IH	Obstructive airway hemangiomas
≥5 cutaneous IHs	Liver hemangiomas, cardiac failure, hypothyroidism
Functional impairment :	
Periocular IH (>1 cm)	Astigmatism, anisometropia, proptosis, amblyopia
IH involving lip or oral cavity	Feeding impairment
Ulceration:	
Segmental IH: IH of any size involving any of the following sites: lips, columella, superior helix of ear, gluteal cleft and/or perineum, perianal skin, and other intertriginous areas (eg, neck, axillae, inguinal region)	Increased risk of ulceration
Associated structural anomalies:	
Segmental IH of face or scalp	PHACE syndrome
Segmental IH of lumbosacral and/or perineal area	LUMBAR syndrome
Disfigurement :	
Segmental IH, especially of face and scalp	High risk of scarring and/or permanent disfigurement
Facial IH (measurements refer to size during infancy): nasal tip or lip (any size) or any facial location ≥2 cm (>1 cm if ≤3 mo of age)	Risk of disfigurement via distortion of anatomic landmarks and/or scarring and/or permanent skin changes
Scalp IH >2 cm	Permanent alopecia (especially if the hemangioma becomes thick or bulky); profuse bleeding if ulceration develops (typically more bleeding than at other anatomic sites)
Neck, trunk, or extremity IH >2 cm, especially in growth phase or if abrupt transition from normal to affected skin (ie, ledge effect); thick superficial IH (eg, ≥2 mm thickness)	Greater risk of leaving permanent scarring and/or permanent skin changes depending on anatomic location
Breast IH (female infants)	Permanent changes in breast development (eg, breast asymmetry) or nipple contour

Categorization of IH as high risk is based on published literature (including the AHRQ review and hemangioma severity scores).

Key Action Statement 1B. After identifying an IH as high risk, facilitate evaluation by a hemangioma specialist as soon possible.

The purpose of this statement is to ensure timely evaluation by a hemangioma specialist of an IH identified as high risk.
After identifying an IH as high risk, clinicians should facilitate an evaluation by a hemangioma specialist as soon as possible.

IH is a disease with a window of opportunity in which to intervene and prevent poorer outcomes, and this critical time frame for optimizing outcomes can be missed if there are delays in referral or treatment. Recent literature suggests that the presence and growth of IHs is apparent much earlier than originally thought.
Premonitory findings appear in the skin during early infancy, including localized blanching or macular telangiectatic erythema.
As endothelial cell proliferation continues, the IH enlarges, becomes more elevated, and develops a rubbery consistency. IHs typically have their clinical onset before 4 weeks of age.
Several studies have helped to better characterize the proliferative phase of IHs. Although IHs proliferate for variable periods of time and to varying degrees, the most rapid growth of superficial IHs typically occurs between 1- and 3-months' chronological age.
IHs reach 80% of their ultimate size by 3 months of age, and the large majority of IHs have completed growth by 5 months of age.
The optimal time for referral or initiation of treatment was 1 month of age, a time far earlier than the time most infants with IHs are typically referred to (or seen by) hemangioma specialists.
Even for the most experienced clinicians, it can be difficult to predict the degree of IH growth until several weeks to months after the lesion is first noticed. By that time, damage to the dermis and subcutaneous tissues as well as permanent distortion of important anatomic landmarks, such as the nose or lips, may already have occurred.
Hence, decisions regarding intervention must be based on risk stratification, including:

- The age of the child (in anticipation of possible IH growth).
- Health considerations (like prematurity).
- Anatomic site.
- The size of the IH.
- Any actual or potential complications.
- Parental preferences.

In high-risk IHs, a wait-and-see approach can result in a missed window of opportunity to prevent adverse outcomes.
On the basis of this information, the consensus recommendation of the subcommittee is:

- that patients with IHs identified as high risk have expedited consultation and/or referral to a hemangioma specialist.
- those who care for infants with IHs should have mechanisms in place to expedite such appointments, including the education of office staff to give young infants with high-risk IHs priority appointments.

Imaging

Key Action Statement 2A

Clinicians should not perform imaging unless:

- **The diagnosis of IH is uncertain:**

Most IHs can be diagnosed clinically. Therefore, imaging of IHs is not indicated for diagnostic purposes unless the lesion has an atypical appearance (ie, the diagnosis is uncertain) or it behaves in a manner that is inconsistent with the expected proliferative growth and involution phases within the expected time frame.

Occasionally, differentiating an IH from a highly vascularized malignant tumor may be difficult. Clinical history, response to therapy, and imaging characteristics considered together are extremely important in this differentiation.

- **There are 5 or more cutaneous His:**

Clinicians should use imaging, specifically abdominal ultrasonography, if 5 or more cutaneous IHs are present to screen for hepatic IH. 30 Ultrasonography has a sensitivity of 95% for detection of hepatic hemangiomas and avoids the need for sedation and exposure to ionizing radiation. 46 Early detection of these lesions may lead to improved monitoring and initiation of appropriate treatment, resulting in decreased morbidity and mortality.

- **Associated anatomic abnormalities are suspected:**

Imaging also is indicated if concern exists for structural anomalies, as would be the case in infants at risk for PHACE syndrome or LUMBAR syndrome. These infants would typically have large (eg, >5 cm in diameter) segmental facial or scalp IHs or segmental IHs of the perineum, gluteal cleft, or lumbosacral area, with or without lower extremity His.

-Noninvasive imaging may be used to monitor response to treatment but typically is not required.

Key Action Statement 2B

- Clinicians should perform ultrasonography as the initial imaging modality when the diagnosis of IH is uncertain.

- Ultrasonography (with Doppler imaging) is the initial imaging modality of choice when the diagnosis of IH is uncertain.

- On ultrasonography, most IHs appear as a well-defined mass with high flow vascular characteristics and no arteriovenous shunting (an exception to the latter is that hepatic IHs may exhibit arteriovenous shunting).

Doppler ultrasonography is also the modality of choice when screening for hepatic IHs and can be used to monitor progression of disease and response to treatment.

Key Action Statement 2C

- Clinicians should perform MRI when concerned about associated structural abnormalities (eg, PHACE syndrome or LUMBAR syndrome).
- Imaging for associated structural anomalies is indicated in infants at risk for PHACE syndrome or LUMBAR syndrome. For example, an infant with a large (eg, >5 cm in diameter) segmental facial or scalp IH is at risk for PHACE syndrome, and further evaluation with MRI and/or magnetic resonance angiography (MRA) of the head and neck (including the aortic arch and brachiocephalic origins) and echocardiography is advisable.
- For patients with segmental IHs of the perineum, gluteal cleft, or lumbosacral area (with or without lower extremity IHs), imaging for LUMBAR syndrome should be considered.
- If there is uncertainty about whether there is a risk of associated structural anomalies, consultation with a hemangioma specialist or other appropriate expert (eg, pediatric neurologist, neurosurgeon, or radiologist) can be helpful to determine if imaging is required and which studies should be performed.
- MRI is the optimal imaging modality to define underlying structural abnormalities, and contrast is needed to assess vascular components.
- MRA can illustrate the vascular anatomy.
- Thus, MRI and MRA, with and without contrast of the head and neck, are the best studies to detect PHACE syndrome.
- In patients in whom there is a risk of LUMBAR syndrome, spinal ultrasonography (for those with a corrected age of less than 6 months) and Doppler ultrasonography of the abdomen and pelvis can be used as an initial screen for abnormalities. Ultimately, however, MRI likely will be

required to provide greater definition. For example, if a high suspicion for spinal abnormalities remains despite normal ultrasonography (ie, there are associated markers of dysraphism [eg, sacral dimple, skin appendage, tuft of hair, and lipoma]), MRI is a more sensitive diagnostic modality.

- Computed tomography is not the modality of choice for imaging IHs because it involves ionizing radiation, which should be avoided in children, particularly young infants, unless absolutely necessary. Advantages of computed tomography are that it can be rapidly performed and may not require sedation.

MANAGEMENT: PHARMACOTHERAPY

Key Action Statement 3A

- Clinicians should use oral propranolol a systemic treatment.
- The oral propranolol is the current treatment of choice for IHs requiring systemic therapy.
- The precise mechanisms of action of propranolol on IHs are unclear but have been hypothesized to be attributable to vasoconstriction, angiogenesis inhibition, induction of apoptosis, inhibition of nitric oxide production, and regulation of the renin-angiotensin system.
- This therapy has now replaced the previous gold standard therapy for threatening IHs, systemic or intralesional corticosteroids.
- The mean estimate of expected clearance for oral propranolol was 95%, which was superior to other interventions.
- a randomized controlled trial (RCT) of oral propranolol compared with observation for IHs, the overall efficacy of propranolol (defined as excellent, good, or medium response) was 98.97%, compared with 31.25% in the observation group ($P < .05$).
- Last, Aly et al 74 compared oral propranolol alone versus oral propranolol combined with 2 weeks of “priming” with oral prednisolone. Those in the prednisolone-primed propranolol group showed a statistically superior reduction in IH size at weeks 2, 4, and 8 compared with the propranolol group, but the 6-month response was equivocal for both groups regarding all assessed variables.

Key Action Statement 3B

- Clinicians should dose propranolol between 2 and 3 mg/kg per day unless there are comorbidities (eg, PHACE syndrome) or adverse effects (eg, sleep disturbance) that necessitate a lower dose.
- The propranolol hydrochloride oral solution (5 mg/mL) recommends a starting dose of 0.5 mg/kg twice daily, with a gradual increase over 2 weeks to a maintenance dose of 1-1.5 mg/kg twice daily (2-3 mg/kg per day based on expression as the hydrochloride salt of propranolol).
- Data comparing 2 and 3 mg/kg per day are lacking.
- Similarly, available data do not permit evidence-based recommendations on dosing frequency (twice daily versus 3 times daily), but both the FDA and the European Medicine Evaluation Agency labeling is for twice-daily dosing.
- The site for initiation of propranolol (outpatient versus inpatient) is evolving as more evidence accumulates that cardiovascular and other acute toxicities occur rarely. Although in both the aforementioned consensus articles, initiation in an inpatient setting is favored.
- In the AHRQ review, the duration of propranolol treatment ranged from 3 to 13 months.
- Rebound growth during tapering or after stopping the medication may occur in 10% to 25% of patients and can occur even after 6 months of therapy.

- A large multicenter retrospective cohort study found the greatest risk of rebound occurred in those in whom therapy was discontinued at <12 months of age (and especially before 9 months), and the lowest risk was in those in whom treatment was discontinued between 12 and 15 months of age.
- Risk factors for rebound growth noted in this study were the presence of mixed or deep morphology and female sex. These observations have led many experts to recommend continuing therapy until at least 1 year of age.
- Dosing may need to be modified in certain situations, these patients include:
    - Those with progressive IH ulceration while receiving therapy and those who experience adverse effects (such as sleep disturbances, High BP).
    - Patients with PHACE syndrome may have an increased risk of stroke, and this risk may be greater if certain neurovascular anomalies are present. In patients who merit systemic IH therapy, the benefits and risks must be carefully weighed. Evaluation with MRI and/or MRA of the head and neck and echocardiography should be performed before or shortly after the initiation of therapy.
- If patients who are at high risk require treatment with propranolol, it is advisable to use the lowest effective dose, slowly titrate the dose, and administer the drug 3 times daily (to minimize abrupt changes in blood pressure); comanagement with a pediatric neurologist is recommended.

Key Action Statement 3C

- Clinicians should counsel that propranolol be administered with or after feeding and that doses be held at times of diminished oral intake or vomiting to reduce the risk of hypoglycemia and hypoglycemia-induced seizures.
- The association between hypoglycemia and propranolol in infants and children is well established and is related to effects on glycogenolysis and gluconeogenesis. β-blockade by propranolol can affect these processes, and infants and children may be particularly susceptible to this effect.
- Early clinical features of hypoglycemia in infants, which may be masqueraded by β-adrenergic blockade, include sweating, tachycardia, shakiness, and anxious appearance, whereas later manifestations (signs of neuroglycopenia) may include lethargy, poor feeding, apnea, seizures, stupor, and loss of consciousness.
- Rates of clinically important harms (hypoglycemia, hypotension, bradycardia, and bronchospasm) varied widely, and the authors assigned a moderate SOE for the association of propranolol with both clinically important and minor harms (with high study limitations). 46 Harms overall did not cause treatment discontinuation. The subcommittee's additional review yielded 8 reports that met inclusion criteria for harms regarding oral propranolol for treatment of IHs.
- These reports provided more detailed information about the occurrence of hypoglycemia. Three of the 8 articles reported hypoglycemia; these articles included 1021 patients, 10 of whom experienced hypoglycemia (3 of these suffered hypoglycemic seizures in the setting of viral gastroenteritis and poor oral intake).
- In a large meta-analysis of oral propranolol for IHs not included in the AHRQ review, adverse events were reported for 1945 of 5862 patients who were treated.
- The investigators identified 24 cases of hypoglycemia and 2 cases of hypoglycemic seizures among 3766 patients who were treated with propranolol from their literature review (some of whom are included in a forementioned studies). Of the 14 events with resolution details, 9 led to dose adjustment or temporary discontinuation of propranolol, and 1 led to permanent discontinuation of treatment. The authors mention that 1 case of hypoglycemic seizure was

related to overdose, and the other was associated with diminished oral intake because of infection.

- Although the risk of hypoglycemia must be considered when prescribing oral propranolol for IHs, routine glucose screening is not indicated. 1,61
- Hypoglycemia occurs infrequently and can be minimized with appropriate education of caregivers on the importance of administering propranolol during or immediately after a feeding and of temporarily withdrawing therapy during periods of fasting (including poor oral intake because of illness or before general anesthesia) or vomiting. 60 Prolonged fasting should be avoided, and parents should be advised that hypoglycemia becomes more likely after ≥8 hours of fasting in infants and young children.

Key Action Statement 3D

- Clinicians should evaluate patients for and educate caregivers about potential adverse effects of propranolol, including sleep disturbances, bronchial irritation, and clinically symptomatic bradycardia and hypotension.
- Adverse effects most frequently reported included sleep disturbances, cold extremities, gastrointestinal symptoms, bronchial irritation (classified as hyperreactivity, bronchospasm, bronchiolitis, and cold-induced wheezing), and a decrease in heart rate or blood pressure.
- Rates of clinically important harms (hypoglycemia, hypotension, bradycardia, and bronchospasm) varied widely across the studies.
- Overall, harms did not cause treatment discontinuation.
- Sleep disturbance, sleeping disorders, agitation during the night, and nightmares or night terrors were mentioned and occurred in 2% to 18.5% of patients who were treated. Propranolol treatment was modified (reduction in dosage, earlier-evening dosing, and early discontinuation of therapy) in response to these effects.
- Although bradycardia and hypotension are known to accompany propranolol-associated β-receptor blockade, both tend to be mild and asymptomatic in children treated for IHs who have no preexisting cardiac comorbidities. In the subcommittee's review, only 1 of the 8 reports mentioned hypotension or bradycardia as an adverse event, with 1 of 906 patients (0.1%) exhibiting bradycardia and 2 of 906 exhibiting asymptomatic hypotension.
- **The use of pretreatment electrocardiography (ECG) is advocated, with brief hospitalization for medication initiation.** several studies have revealed no actionable findings with continuous ECG monitoring, and researchers have questioned its value. FDA guidelines for patient monitoring do not include routine ECG. In their consensus recommendations, ECG screening only.
- (1) in infants with a baseline heart rate below normal for age,
- (2) in infants with a family history of congenital heart conditions or arrhythmias or with a maternal history of connective tissue disease,
- (3) when there is a history of arrhythmia, or one is auscultated during examination.

Key Action Statement 3E

- Clinicians may prescribe oral prednisolone or prednisone to treat IHs if there are contraindications or an inadequate response to oral propranolol.
- Systemic therapy with corticosteroids was considered the standard of care for several decades before being supplanted by oral propranolol. In the AHRQ review, oral steroids had a mean estimate of expected clearance of 43%. The AHRQ report identified 24 studies (3 RCTs, 1 cohort study, and 20 case series) reporting outcomes and/or harms after corticosteroid use in children

with IHs. One RCT was judged as good, 1 as fair, and 1 as poor quality, and the cohort study was judged as fair quality (all case series were judged as poor quality for harms reporting).

- The steroids studied varied in terms of dose, type, route of administration, and patient ages. Children in steroid treatment arms typically had modest improvement in lesion size, but outcomes were difficult to compare given differences in scales.
- The optimal dosing of systemic corticosteroids for IHs remains unclear. Dose ranges of prednisone or prednisolone reported most frequently in the literature are between 2 and 5 mg/kg per day, and most consider optimal dosing to be 2 to 3 mg/kg per day. Typical protocols include treating at full dose for 4 to 12 weeks followed by a gradual taper and completion of therapy by 9 to 12 months of age.
- In the AHRQ review, steroids were consistently associated with clinically important harms, including Cushingoid appearance, infection, growth retardation, hypertension, and mood changes. The authors considered the SOE to be moderate for the association of steroids with clinically important harms.

Key Action Statement 3F

- Clinicians may recommend intralesional injection of triamcinolone and/or betamethasone to treat focal, bulky IHs during proliferation or in certain critical anatomic locations (eg, the lip).
- Numerous studies have reported success in the use of steroid injections for IHs, demonstrating it to be safe and effective.
- This modality is most often reserved for IHs that are relatively small and well localized where proliferation is resulting in increased bulk and threatening anatomic landmarks (eg, the lip or nose). Larger or more extensive lesions are poorer candidates for this treatment modality given the larger volume of steroids necessary (and the inherent systemic risks), the difficulty of obtaining even distribution throughout the tumor, and the potential for local complications in lesions that are mostly flat or superficial.
- 3 Most studies have used triamcinolone either alone or in conjunction with betamethasone, with injections given on average every 4 to 6 weeks (but with wide variability). Repeat injections are often administered, with the number used ranging in most reports from 1 to 7.
- The AHRQ review found that intralesional triamcinolone had a mean estimate of expected clearance of 58% (Table 12). Overall, the SOE was low for intralesional steroids having a modest effect relative to control, with wide confidence bounds.
- This was a retrospective review of patients with periocular IHs treated with oral propranolol, who were compared with a cohort treated with intralesional corticosteroid injection. Both groups showed a reduction in astigmatism over 12 months, and neither experienced significant adverse effects necessitating dose reduction or treatment cessation. The authors concluded that oral propranolol (given its efficacy and safety profiles) has emerged as the treatment of choice for periocular IHs requiring therapy. 115 Steroids (oral and intralesional forms were grouped together in the AHRQ harms analysis) were consistently associated with clinically important harms, including Cushingoid appearance, infection, growth retardation, hypertension, and mood changes. The authors considered the SOE to be moderate for the association of steroids with clinically important harms.
- The most commonly reported complications associated with intralesional steroid injection for IHs are transient Cushingoid features, failure to thrive, and local skin complications.
- Local complications may include fat and/or dermal atrophy and pigmentary changes.
- Adrenal suppression is infrequently reported in association with intralesional steroid injections but has been observed when large doses (eg, >4 mg/kg) have been administered.

Key Action Statement 3G

- Clinicians may prescribe topical timolol maleate as a therapy for thin and/ or superficial IHs.
- Topical timolol maleate, a nonselective β-adrenergic receptor inhibitor, has been used in the treatment of pediatric glaucoma as a first-line agent for several decades.
- Treatment of IHs with ophthalmic timolol maleate was initially reported in 2010, and since that time, there have been many reports (including some with hundreds of patients), as well as an RCT, with positive findings.
- Based on these reports showing efficacy with minimal adverse effects, timolol is increasingly being used for thin and superficial IHs, and many centers report that their use of timolol exceeds that of oral β-blockers.
- In the AHRQ review, 2 RCTs and 4 cohort studies were included. Topical timolol had a mean estimate of expected clearance of 62%.
- Timolol was significantly more effective than observation or a placebo in 3 studies; 1 study comparing topical imiquimod with timolol did not demonstrate superiority of either agent but was found to have insufficient SOE. In the largest of these, a multicenter retrospective cohort study of 731 patients, most infants were treated with the 0.5% gel-forming solution. The study reveal improvement in nearly 70% of patients treated for 1 to 3 months and in 92.3% of patients who received 6 to 9 months of therapy. The greatest improvement was in color; however, with a longer duration of treatment, improvement in size, extent, and volume were also observed. Best responses were observed in thinner superficial IHs (ie, < 1 mm thick) versus mixed or deep IHs.
- The large majority of infants studied were 6 months or younger at time of initiation of treatment, and 41% were ≤3 months of age. This suggests that early topical timolol treatment may also inhibit IH growth. Only 7% of infants required subsequent treatment with a systemic β-blocker.
- Although pharmacokinetic data are limited, evidence suggests that timolol maleate can be detected in the blood or urine of at least some infants treated topically. Additional pharmacokinetic studies are needed given occasional reports of systemic toxicity. In the large cohort study of 731 patients, adverse events were noted in 3.4% of patients and included local irritation (nearly half of the adverse events) and bronchospasm (in 3 patients); no cardiovascular events were reported. No adverse events were significant enough to necessitate drug discontinuation.
- To address concerns regarding potential percutaneous absorption and toxicity, many authors have advocated using limited amounts of medication (eg, 1 drop 2–3 times per day), and some have cautioned against application to ulcerated lesions.

SURGICAL MANAGEMENT

Key Action Statement 4

- Clinicians may recommend surgery and laser therapy as treatment options in managing selected IHs (grade C, moderate recommendation).
- With the advent of β-blocker therapy, surgical and laser approaches are used less frequently.
- In general, surgical interventions are not performed in infancy. During this time, anesthetic risks are of greater concern, and the tumor is highly vascular, posing a higher risk of blood loss, iatrogenic injury, and an inferior outcome.
- In certain locations, such as the lip and nasal tip, the final cosmetic result is superior when growth of the lesion has ceased, and the number of surgical interventions can be kept to a minimum. Furthermore, there is no psychosocial urgency to improve a deformity caused by IHs in this age group because long-term memory and self-esteem are not established until later in childhood.

- There are certain clinical situations, however, in which early surgery can be an important treatment option. These include IHs that ulcerate, obstruct or deform vital structures (such as the airway or orbit), or involve aesthetically sensitive areas. In these circumstances, surgery may be indicated when:
  (1) the lesion has failed to improve with local wound care and/or pharmacotherapy.
  (2) the lesion is well localized, and early surgery will simplify later reconstruction (eg, a prominent IH involving the ear or eyelid [causing ptosis]).
  (3) the lesion is well localized in an anatomically favorable area; or
  (4) resection is likely to be necessary in the future, and the resultant scar would be the same.

- The decision to undertake surgery during infancy should take into consideration current knowledge of the risks of general anesthesia in this age group.
- Surgery also is an important treatment option for IHs that, despite involution, have left residual skin changes (eg, thinned skin, scar, fibrofatty tissue, telangiectasias, and/or anatomic deformities in areas such as the nose, ear, or lip).
- In most cases, deferring surgery until the child is 3 to 5 years of age is reasonable because:
  (1) the lesion may resolve significantly without leaving a deformity that necessitates intervention.
  (2) the tumor is smaller than it was during infancy, and thus, the operation is often easier, and the resultant scar may be smaller; and
  (3) the IH primarily is adipose tissue instead of blood vessels, and thus, the operation is safer.

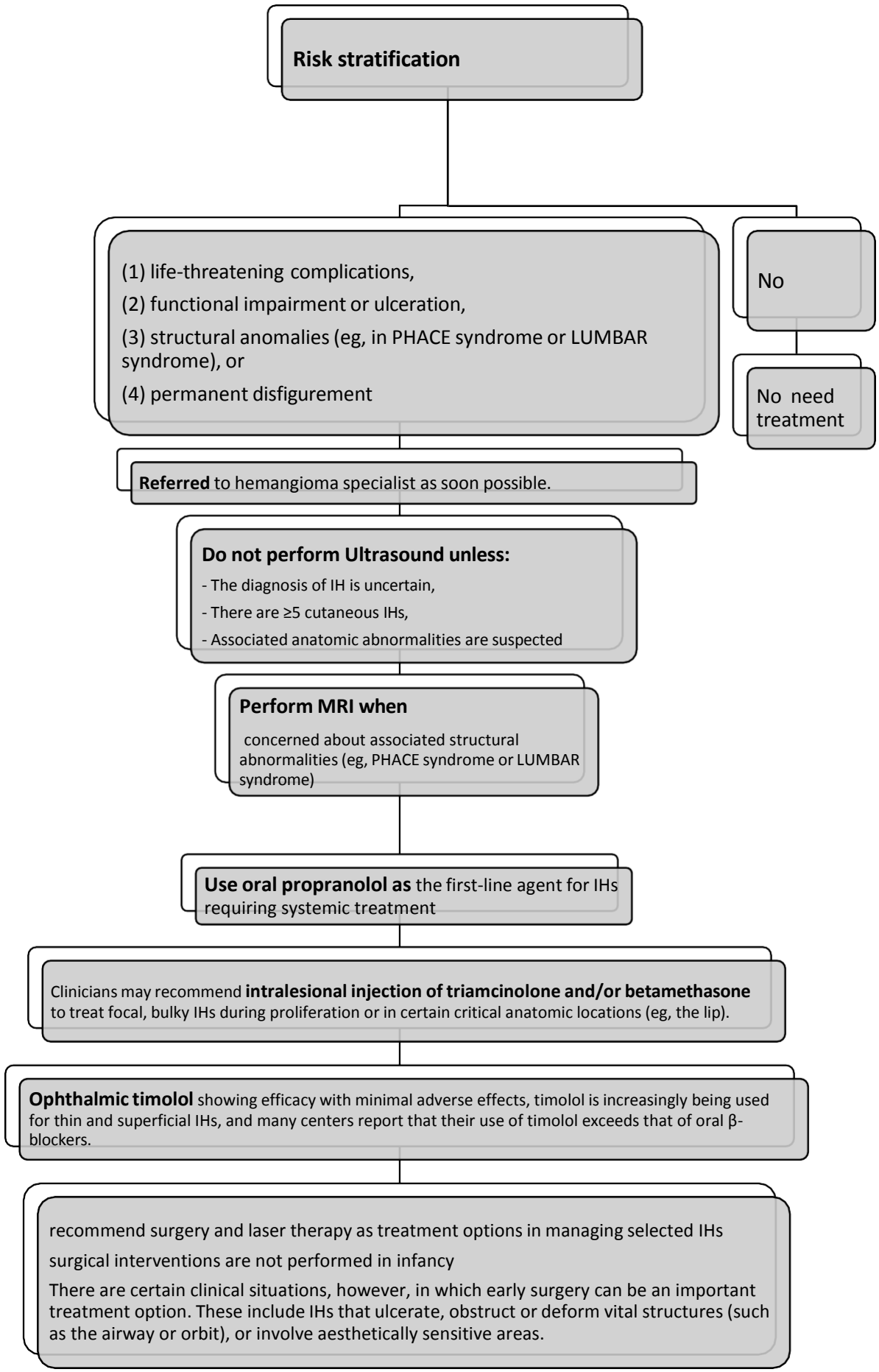
- However, it is usually unnecessary to wait longer than 3 to 5 years of age because the previously accepted adage that 50% of IHs complete involution by 5 years of age, 70% by 7 years of age, and 90% by 9 years of age has proven to be incorrect.
- In fact, most IHs do not improve significantly after 3 to 4 years of age. Moreover, performing surgery at this earlier age can be beneficial in minimizing stigma and impact on a child's self-esteem.
- There is less urgency to correct a residual deformity in an area that is concealed by clothing (eg, a lesion on the trunk). Some parents may elect to wait until the child is older and able to help in decision-making, especially if the reason for surgery is the management of less disfiguring skin changes.
- Laser Management PDL has been used for several decades to treat IHs. The AHRQ review noted that most studies that were reviewed evaluated PDL (as opposed to other lasers) and examined heterogeneous end points (the latter factor limiting the ability to draw conclusions).
- However, there is low SOE that PDL is more effective in reducing IH size when compared with observation.
- There is evidence that PDL is superior to other lasers. In contrast, there is wide recognition that PDL is effective and safe in removing residual macular erythema and superficial telangiectasias in involuting or involuted IHs, but it often requires several treatments to achieve optimal results. Other lasers, such as erbium-yttriumaluminum-garnet, have been reportedly effective in ameliorating textural changes in small case series.
- Harms associated with laser therapy that were identified in the AHRQ review included skin atrophy, bleeding, scarring, ulceration, purpura, and pigmentation changes.
- There is controversy regarding whether PDL should be used to treat IHs early in infancy (ie, during the proliferative phase). Several case reports and case series have revealed an increased risk of ulceration, scarring, and hypopigmentation when PDL is used during this period. Moreover, PDL penetrates only into the superficial dermis, and thus, although redness

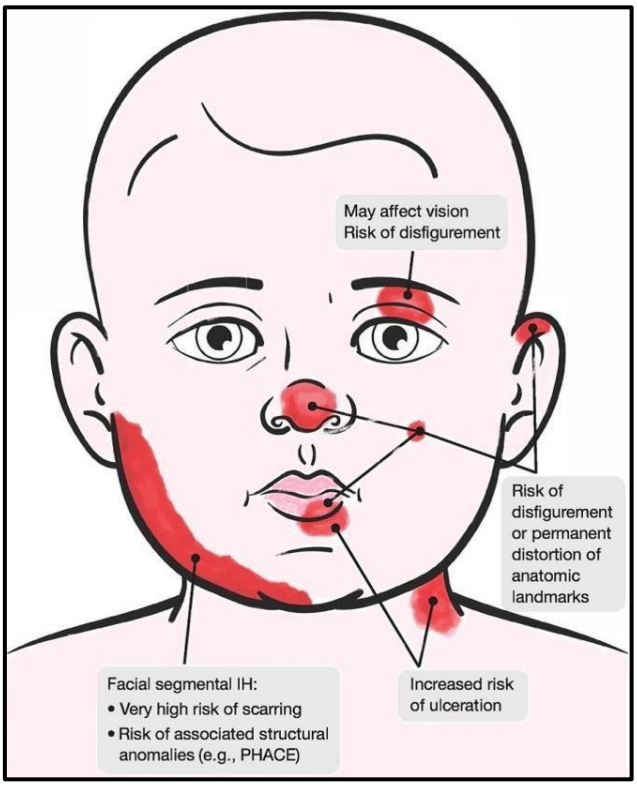
may be diminished, deeper elements of the IH (that increase the risk of residual skin changes) are not affected.

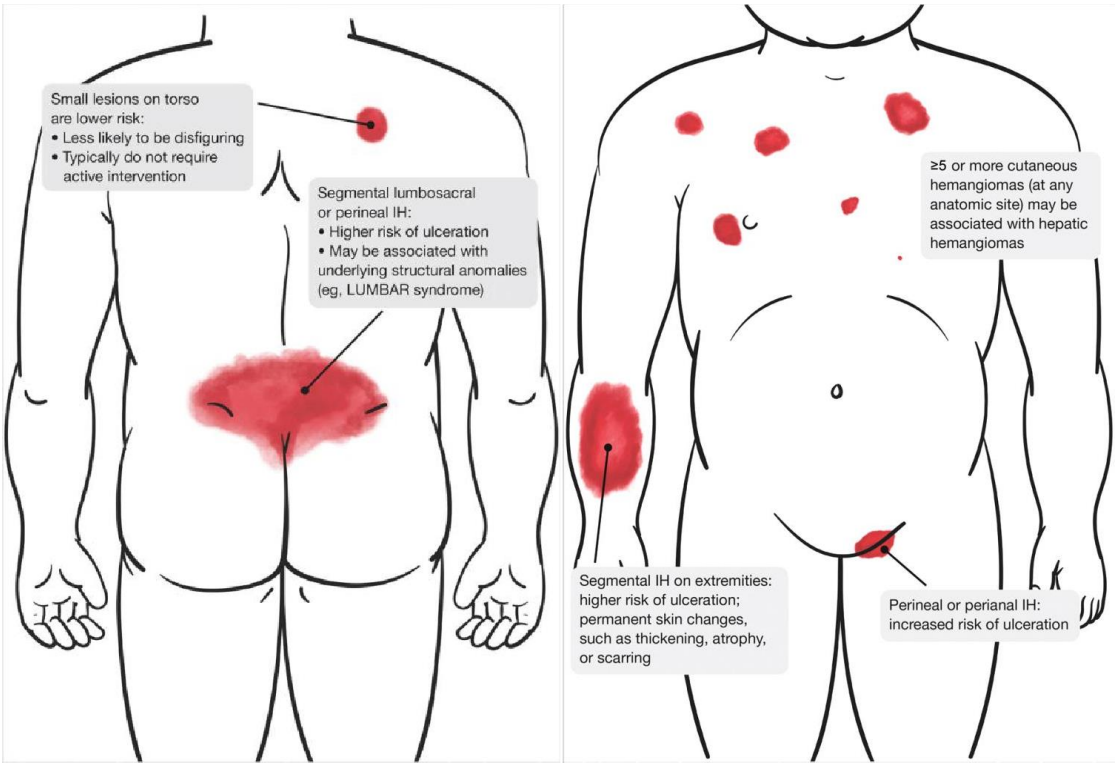
- Some authors advocate for using PDL as a treatment of ulceration. However, evidence supporting the use of PDL for this indication comes from case reports and small case series. Propranolol has been associated with faster healing of ulceration when compared with laser therapy and antibiotics.

PARENT EDUCATION Key Action Statement 5

- Clinicians should educate parents of infants with an IH about the condition, including the expected natural history, and its potential for causing complications or disfigurement.
- The information provided by clinicians should be as specific to the patient's IH as possible (eg, indicating whether and why an IH is low risk and, thus, likely to cause no problems or sequelae or is potentially high risk and requires urgent evaluation or treatment.
- Formal educational efforts can reduce parental anxiety and enhance comfort with a plan to observe the IH for any unexpected or worrisome changes.
- Parents should be educated about the natural history of IHs. Specifically, they may be advised that, although growth characteristics vary from case to case, most superficial IHs have a maximum growth potential between 1 and 3 months of age, and that the majority of growth is complete by 5 months of age.
- Deeper IHs may have a slightly later onset and a more prolonged duration of growth. During the period of growth, clinicians should encourage parents to call, schedule an office visit, or share photographs of the IH with them to reassess if concerns exist about the lesion's appearance, unexpectedly rapid growth, ulceration, bleeding, or pain, all findings that indicate that a lesion is no longer low risk. Parents should be advised that by age 5 to 12 months, most IHs have stopped growing and are beginning to involute.
- For IHs with a superficial component, this appears as a gradual change in color from red to milky-white or gray. Lesions gradually flatten and shrink from the center outward. Involution proceeds more slowly than growth.
- Newer studies have demonstrated that 90% of IH involution is complete by 4 years of age.
- This is in contrast to traditional teaching that involution proceeds at 10% per year (ie, 50% of IHs resolve by 5 years of age and 90% by 9 years of age).
- Parents should be advised that even after involution, residual changes, such as telangiectasias, redundant skin, or a scar, may be left.
- It is usually possible to tell whether such changes are going to persist by 4 years of age, and if concerning, consultation for management of these skin changes, particularly laser or surgical treatment, may be pursued.
- A collection of serial photographs can be useful to demonstrate to parents the natural history of IHs and the process of spontaneous involution.


Risk stratification
(1) life-threatening complications,
(2) functional impairment or ulceration,
(3) structural anomalies (eg, in PHACE syndrome or LUMBAR syndrome), or
(4) permanent disfigurement
No
No need treatment
Referred to hemangioma specialist as soon possible.
Do not perform Ultrasound unless:
- The diagnosis of IH is uncertain,
- There are ≥5 cutaneous IHs,
- Associated anatomic abnormalities are suspected
Perform MRI when
concerned about associated structural abnormalities (eg, PHACE syndrome or LUMBAR syndrome)
Use oral propranolol as the first-line agent for IHs requiring systemic treatment
Clinicians may recommend intralesional injection of triamcinolone and/or betamethasone to treat focal, bulky IHs during proliferation or in certain critical anatomic locations (eg, the lip).
Ophthalmic timolol showing efficacy with minimal adverse effects, timolol is increasingly being used for thin and superficial IHs, and many centers report that their use of timolol exceeds that of oral β-blockers.
recommend surgery and laser therapy as treatment options in managing selected IHs
surgical interventions are not performed in infancy
There are certain clinical situations, however, in which early surgery can be an important treatment option. These include IHs that ulcerate, obstruct or deform vital structures (such as the airway or orbit), or involve aesthetically sensitive areas.


May affect vision
Risk of disfigurement
Risk of disfigurement or permanent distortion of anatomic landmarks
Facial segmental IH:
• Very high risk of scarring
• Risk of associated structural anomalies (e.g., PHACE)
Increased risk of ulceration


Small lesions on torso are lower risk:
• Less likely to be disfiguring
• Typically do not require active intervention
Segmental lumbosacral or perineal IH:
• Higher risk of ulceration
• May be associated with underlying structural anomalies (eg, LUMBAR syndrome)
≥5 or more cutaneous hemangiomas (at any anatomic site) may be associated with hepatic hemangiomas
Segmental IH on extremities: higher risk of ulceration; permanent skin changes, such as thickening, atrophy, or scarring
Perineal or perianal IH: increased risk of ulceration

Dose of propranolol between 2 and 3 mg/kg per d unless there are comorbidities (eg, PHACE syndrome) or adverse effects (eg, sleep disturbance) that necessitate a lower dose

The propranolol hydrochloride oral solution (5 mg/mL) recommends a starting dose of 0.5 mg/kg twice daily, with a gradual increase over 2 weeks to a maintenance dose of 1-1.5 mg/kg twice daily

Propranolol be administered with or after feeding and that doses be held at times of diminished oral intake or vomiting to reduce the risk of hypoglycemia

Evaluate patients for sleep disturbances, bronchial irritation, and clinically symptomatic bradycardia and hypotension

The use of pretreatment continuous ECG monitoring is advocated, with brief hospitalization for medication initiation.

the duration of propranolol treatment ranged from 3 to 13 months. to recommend continuing therapy until at least 1 year of age.

Dosing may need to be modified in certain situations, these patients include:

- Those with progressive IH ulceration while receiving therapy and those who experience adverse effects (such as sleep disturbances, High BP).

- Patients with PHACE syndrome may have an increased risk of stroke, and this risk may be greater if certain neurovascular anomalies are present. In patients who merit systemic IH therapy, the benefits and risks must be carefully weighed.

Reference:

Krowchuk DP, Frieden IJ, Mancini AJ, et al. Clinical Practice Guideline for the Management of Infantile Hemangiomas, American Academy of Pediatrics. PEDIATRICS J Volume 143, number 1, January 2019:e20183475

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