Diagnosis and Management of Infantile Hemangioma

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abstract

Infantile hemangiomas (IHs) are the most common tumors of childhood. Unlike other tumors, they have the unique ability to involute after proliferation, often leading primary care providers to assume they will resolve without intervention or consequence. Unfortunately, a subset of IHs rapidly develop complications, resulting in pain, functional impairment, or permanent disfigurement. As a result, the primary clinician has the task of determining which lesions require early consultation with a specialist. Although several recent reviews have been published, this clinical report is the first based on input from individuals representing the many specialties involved in the treatment of IH. Its purpose is to update the pediatric community regarding recent discoveries in IH pathogenesis, treatment, and clinical associations and to provide a basis for clinical decision-making in the management of IH.

NOMENCLATURE

The nomenclature and classification of vascular tumors and malformations have evolved from clinical descriptions ("strawberry birthmark," "salmon patch," "cavernous hemangioma," and "port wine stain") to terminology based on their cellular features, natural history, and clinical behavior. Originally described by Mulliken and Glowacki in 1982, the most current and widely accepted classification of vascular anomalies is that adopted by the International Society for the Study of Vascular Anomalies (Table 1). This system includes infantile hemangioma (IH) among the vascular neoplasms, which are lesions characterized by abnormal proliferation of endothelial cells and aberrant blood vessel architecture. In contrast, vascular malformations are structural anomalies and inborn errors of vascular morphogenesis.

Although IH is the most common neoplasm, this group also includes such tumors as congenital hemangiomas, pyogenic granulomas, tufted angiomas (TAs), and several types of hemangioendothelioma. Congenital hemangiomas are biologically and behaviorally distinct from IH. As reflected in the name, congenital hemangiomas are present and fully formed at birth; they do not exhibit the postnatal proliferative phase
characteristic of IH. The 2 variants are the noninvoluting congenital hemangioma (NICH), which remains stable without growth or involution,2,3 and the rapidly involuting congenital hemangioma (RICH), which undergoes a rapid involution phase beginning in the first year of life (Fig 1).4 RICHs, in some cases, have been associated with thrombocytopenia but with milder and more transient coagulopathy than that seen in Kasabach-Merritt phenomenon (KMP; see discussion that follows); rarely, they can be associated with congestive heart failure.5,6 Some RICHs show incomplete involution, and it is possible that RICH and NICH lie at opposite ends of the same clinical spectrum.7,8 Both subtypes of congenital hemangioma were initially believed to be variants of IH that exhibited prenatal growth until North et al9 showed that, unlike IH, neither lesion expresses glucose transporter protein isoform 1 (GLUT1).

Pyogenic granuloma, also known as lobular capillary hemangioma, is neither pyogenic nor granulomatous.

It is a reactive proliferating vascular lesion that is classified as a vascular neoplasm (Table 1). This common acquired vascular lesion of the skin and mucous membranes primarily affects infants and children and is frequently misdiagnosed as IH. Approximately 12% occur in infancy, and 42% present during the first 5 years of life.10 Pyogenic granulomas are most commonly located on the head and neck, rapidly enlarge to a median size of 6.5 mm, frequently develop a pedunculated base, and, with erosion, are prone to bleeding that is difficult to control (Fig 2).10 Pyogenic granulomas are seen with higher frequency within the skin containing capillary malformations.

Two other distinct benign vascular neoplasms, kaposiform hemangoendothelioma (KHE) and TA, have been confused with IH. KHE presents primarily in infancy but with a far wider age range than IH, which is usually apparent in the first month of life. KHE is considered a locally aggressive neoplasm that typically appears as a deep, soft tissue mass. This lesion has been associated with KMP,11 a potentially life-threatening consumptive coagulopathy characterized by severe platelet trapping. Before KHE was described in the early 1990s, KMP was erroneously thought to occur in association with IH.

Histopathologically, KHE shows infiltrating sheets of slender, GLUT1-negative endothelial cells lining slitlike capillaries.12 TAs are benign vascular tumors that occur in infants, children, or young adults and are usually located on the neck or the upper part of the thorax.13 Their clinical appearance is variable and includes erythematous to violaceous patches, plaques, and nodules. Histopathologically, TA shows well-defined tufts of capillaries in the dermis that lack cellular atypia or GLUT1 positivity and, like KHE, is associated with increased lymphatic vessels and a predisposition to KMP. Both tumors behave unpredictably and may grow slowly over the course of months to years, grow rapidly, spontaneously regress, or remain dormant for years.14-16 Unlike KHE and TA, IHs are not associated with thrombocytopenia or coagulopathy.

Vascular malformations are congenital lesions, but some may become clinically apparent only later in life, presumably because of slowly progressive ectasia resulting from intraluminal flow. They exhibit a normal rate of endothelial cell turnover throughout their natural history but expand as the patient grows. Vascular malformations do not involute, and their growth may be influenced by trauma, infection, and hormonal changes. Classification is based on the predominant vessel type: capillary or venulocapillary, venous, lymphatic, arterial, or mixed.17 As with vascular neoplasms, the nomenclature of vascular malformations has led to great confusion. Capillary or venulocapillary malformations have had numerous alternative designations, the most common being “port wine stain” and “nevus flammeus.” Venous malformations have often been mistaken for IH,

**TABLE 1** Classification of Cutaneous Vascular Anomalies, 2014

<table>
<thead>
<tr>
<th>Vascular malformations</th>
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<tbody>
<tr>
<td>Venous malformations</td>
</tr>
<tr>
<td>Lymphatic malformations</td>
</tr>
<tr>
<td>Capillary malformations and fistulae</td>
</tr>
<tr>
<td>Mixed (combined) malformations</td>
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</tbody>
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<table>
<thead>
<tr>
<th>Vascular tumors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign</td>
</tr>
<tr>
<td>Infantile hemangioma (IH)</td>
</tr>
<tr>
<td>Congenital hemangioma (rapidly involuting [RICH]; non-involuting [NICH])</td>
</tr>
<tr>
<td>Lobulated capillary hemangiomas (LCH)</td>
</tr>
<tr>
<td>(pyogenic granuloma)*</td>
</tr>
<tr>
<td>Tufted angiomia (TA)</td>
</tr>
<tr>
<td>Others</td>
</tr>
</tbody>
</table>

| Locally aggressive                     |
| Kaposiform hemangoendothelioma (KHE)   |
| Kaposi sarcoma                         |
| Others                                 |

| Malignant                              |
| Angiosarcoma                           |
| Others                                 |

Adapted from the International Society for the Study of Vascular Anomalies, 2014, ref 1 (issva.org/classification).

*Reactive proliferating vascular lesion

**FIGURE 1**

RICH is fully formed at birth (A) and then involutes, mostly during the first year of life. B, The same lesion seen at 8 months of age.
termed “cavernous hemangiomas” and “venous hemangiomas” in the literature (Fig 3A). Lymphatic malformations, which are subdivided into microcystic and macrocystic varieties on the basis of predominant lacuna size, may also be mistaken for IH when there is bleeding into vesicles at the surface of the skin or mucosa (Fig 3B). These lesions have traditionally been referred to as “cystic hygromas” or “lymphangiomas,” designations that inaccurately presume proliferative potential, thereby perpetuating the diagnostic confusion.

The use of various names for IH has resulted in immense diagnostic confusion. For instance, the terms resulted in immense diagnostic confusion. For instance, the terms "capillary hemangioma" and "capillary angioma" have been used to refer to an IH that is located primarily in the dermis and is bright red in color. In contrast, the designations "cavernous" or "venous" have inappropriately been used to define an IH that, because of its depth below the dermis, may impart a blue tinge to the skin surface. In addition, deep venous and lymphatic malformations as well as arteriovenous malformations have been incorrectly diagnosed as deep IH. Finally, by virtue of its sheer prevalence, the term “hemangioma,” without the adjectival descriptor "infantile" or with the descriptor “juvenile,” has been used in reference to IH for many years, especially predating the distinction between IH and the congenital hemangiomas.

“Hemangioma” has also been inappropriately used to describe, in general terms, varieties of other noninfantile hemangiomas and vascular malformations.

**Highlights of This Section**

- Infantile hemangioma (IH) is the currently accepted terminology for the lesions that are the focus of this clinical report.
- Congenital hemangiomas are biologically and behaviorally distinct from IH.
- Pyogenic granuloma is a reactive proliferating vascular lesion that is classified as a vascular neoplasm and that may occasionally be misdiagnosed as IH.
- Lesions diagnosed as “cavernous hemangiomas” are usually, in fact, deep IHs or venous malformations.
- Kasabach-Merritt phenomenon or KMP (a consumptive coagulopathy) is not associated with IH but rather with 2 other vascular neoplasms, kaposiform hemangioendothelioma (KHE) and tufted angioma (TA).

**EPIDEMIOLOGY**

Studies of the incidence of IH, including a prospective study and a review incorporating 1 retrospective study and 2 cross-sectional cohorts, suggest that 4% to 5% of infants are affected. Other studies suggest that IH is observed in 1% to 3% of newborn infants and 2.6% to 9.9% of older children, but methodologic shortcomings may have influenced these findings. IHs are more common among female infants; however, although older data suggest female-to-male ratios ranging from 3:1 to 5:1, more recent studies suggest a range of 1.4:1 to 3:1. The gender discrepancy appears to be increased among children with PHACE syndrome (Posterior fossa defects, Hemangiomas, cerebrovascular Arterial anomalies, Cardiovascular anomalies including coarctation of the aorta, and Eye anomalies), in which studies have found a 9:1 female-to-male ratio. There is not a definitive explanation for this gender difference.

Most studies report a significantly higher incidence in white infants. On the basis of the success of IH treatment using beta-blocker therapy, it has been proposed that black infants may exhibit some form of “endogenous beta blockade,” and there are molecular biological data to support this notion.

The incidence of IH is increased among preterm infants, affecting 22% to 30% of infants weighing less than 1 kg. Multivariate analysis has revealed that low birth weight (LBW) is the major contributor to this risk; there is a 25% increase in risk of developing an IH with every 500-g reduction in birth weight. Prenatal factors have also been investigated for their role in IH. Studies differ regarding an increased risk resulting from maternal chorionic villus sampling or amniocentesis and any increased risk attributable to chorionic villus sampling appears to be limited to procedures performed transcervically. Other possible prenatal factors include older maternal age, multiple gestation pregnancy, placenta previa, and preeclampsia. Placental anomalies, such as retroplacental hematoma, infarction, and dilated vascular communications, have also been associated with IH development. It is theorized that the common thread...
in these associations is placental hypoxia.\textsuperscript{32,33} Although often suggested as a risk factor, a family history of IH is reported in only 12\% of cases\textsuperscript{24}; however, familial clustering has been reported.\textsuperscript{34,35} Associations are also reported with maternal use of fertility drugs,\textsuperscript{36} use of erythropoietin,\textsuperscript{37} level of maternal education,\textsuperscript{36} breech presentation,\textsuperscript{23} and being the first born.\textsuperscript{23}

PATHOGENESIS AND HISTOPATHOLOGY

The pathogenesis of IH, despite intensive study, has not been completely elucidated. Lines of evidence support a cellular origin from either intrinsic endothelial progenitor cells (EPCs) or angioblasts of placental origin, but intrinsic and extrinsic factors are also thought to contribute to their development.\textsuperscript{38} Intrinsic factors include the influence of angiogenic and vasculogenic factors within the IH. External factors include tissue hypoxia and developmental field disturbances. The EPC theory holds that IHs develop from clonal expansion of circulating EPCs, resulting in vasculogenesis, or the de novo formation of new blood vessels.\textsuperscript{39,40} This theory is supported by studies showing increased numbers of circulating EPCs in blood samples from children with IH.\textsuperscript{41} Additional evidence comes from studies in which multipotential stem cells derived from IH specimens (HemSCs) have shown the ability to recapitulate human IH in immunodeficient mice.\textsuperscript{42} These HemSCs and cord blood EPCs behave similarly to each other in several in vitro assays, suggesting that circulating EPCs could be the origin of IH endothelial cells.\textsuperscript{42} The concept that IHs originate from circulating multipotent progenitor cells could explain some of the features they share with placental blood vessels, because dysregulated circulating EPCs have also been implicated in many of the associated maternal and fetal comorbid conditions (preeclampsia, retinopathy of prematurity, etc). HemSCs have also been shown to have an adipogenic potential,\textsuperscript{43} which may explain the presence of adipocytes noted during involution. The stimulus for division of EPCs is unknown but may be a somatic mutation or abnormal signals from local tissues. The theory of placental origin suggests that fetal progenitor cells arise from the disruption of the placenta during gestation or birth.

This concept developed from research showing that molecular markers characteristic of placental tissue, including GLUT1, Lewis Y antigen, merosin, Fc-\gamma receptor-IIb, indoleamine 2,3-deoxygenase, and type III iodothyronine deiodinase, were also present in IHs.\textsuperscript{3,9} Clinical evidence for this theory is suggested by those studies showing an increased incidence of IH in association with chorionic villus sampling, placenta previa, and preeclampsia.\textsuperscript{24,30,31} A unifying theory suggests that IH results from aberrant proliferation and differentiation of a hemogenic endothelium with a neural crest phenotype and a capacity for endothelial, hematopoetic, mesenchymal, and neuronal differentiation. It is hypothesized that placental chorionic villus mesenchymal core cells embolize to the developing fetus and that the timing of this embolization in relation to the migration of neural crest cells along their somitic routes determines the morphology of the IH (segmental versus localized [focal]; see section entitled “Clinical Appearance”).\textsuperscript{44} The cytokine niche within the IH, including vascular endothelial growth factors (VEGFs), insulin-like growth factors, the tumor necrosis factor-related apoptosis-inducing ligand-osteoprotegerin (TRAIL-OPG)
pathway, and the renin-angiotensin system, subsequently regulates growth of the IH and its response to pharmacologic therapies.44 Other authors have also embraced the “niche” concept, suggesting that circulating EPCs find their way to certain locations that provide conditions favorable for growth into placentalike tissues.44 In tissues such as the skin and liver, progenitor cells may encounter the cellular signals and local tissue factors required to stimulate their development.

On the basis of the rapid proliferation of endothelial cells, earlier investigations of IH origin focused on angiogenesis, the sprouting of endothelial cells from existing blood vessels. Such studies have shown an increased concentration of angiogenic factors in IH, such as basic fibroblast growth factor (bFGF), VEGF-A, insulin-like growth factor, and matrix metalloprotease (MMP) 9 within the lesion during proliferation.45 Also in this phase, investigators have identified indoleamine 2,3-deoxygenase, a protein thought to slow the involution of IH by inhibiting cytotoxic T-lymphocyte response.46 During involution, endothelial cell apoptosis is accompanied by downregulation of angiogenic factors, whereas inhibitors of angiogenesis such as interferon-β and markers of cell maturation such as intercellular adhesion molecule 1 are upregulated.47 It has also been shown that involuting IHs exhibit decreased production of nitric oxide, a potentiator of the VEGF pathway, as measured by reduced levels of endothelial nitric oxide synthase.48 It has been hypothesized that hypoxia triggers a vascular response in infants. As discussed above, LBW is a significant risk factor for IH, and in utero hypoxia is a common cause of LBW. Not surprisingly, there is mounting evidence of the role of hypoxia in the development of IH. GLUT1, a facilitative glucose transporter used as a marker for IH, is an important sensor of hypoxia.9 GLUT1 has been shown to be upregulated in hypoxic zones of mesenchymal tumors and in umbilical cord–derived human mesenchymal stem cells under hypoxic conditions.49,50 Hypoxia-induced factors produced by endothelial cells appear to play an important role in trafficking of progenitor cells to ischemic tissue. These factors have been shown to be upregulated in the blood (VEGF-A, MMP-9) and in IH tissue (stromal cell–derived factor 1α, MMP-9, VEGF-A, and hypoxia-inducible factor 1α) from children with proliferating IH.41 In addition, it has been shown that the use of erythropoietin in preterm infants increases the risk of developing an IH.37 Thus, tissue ischemia resulting in neovascularization from circulating EPCs has been proposed as the stimulus leading to the development of IH.41 Clinically, an area of pallor or decreased blood flow in the skin has been noted to precede the development of IH, further supporting this hypothesis.51

Highlights of This Section

- may develop either from intrinsic endothelial progenitor cells (EPCs) or from angioblasts of placental origin.
- IH growth is affected by intrinsic influences, such as angiogenic and vasculogenic factors within the IH, and by external factors such as tissue hypoxia and developmental field disturbances.
- A unifying theory proposes that circulating EPCs migrate to locations in which conditions are favorable for growth into placentalike tissues.

Histopathology

Grossly proliferative and early involuting IHs are well-circumscribed, unencapsulated masses with red-to-tan cut surfaces. Later involuting lesions are fibrofatty in consistency and less defined. The histologic features of IH change dramatically as they proceed through their natural course of neonatal presentation, rapid growth, and subsequent involution, requiring interpretation within the proper clinical context.52-54 There is no sharp dividing line between proliferation and involution, and features of involution typically coexist with features of proliferation during much of the process. Early proliferative phase IHs are composed of well-defined, unencapsulated masses of capillaries lined by plump endothelial cells rimmed by plump pericytes embedded within a multilaminated basement membrane without associated smooth muscle cells (Fig 4). Lesions at this stage may at least focaly resemble other rapidly growing vascular proliferations such as early pyogenic granulomas. The proliferating capillaries are arranged in lobules, separated by delicate fibrous septae or by normal intervening tissue. These lesional capillaries, depending on tissue location, intermingle nondestructively with superficial skeletal muscle fibers, peripheral nerves, salivary glands, and adipocytes. Endothelial cells and pericytes show variably enlarged nuclei and abundant clear cytoplasm. Normally configured mitotic figures are relatively numerous (Fig 1B); and widespread expression of cell proliferation markers, such as Ki-67, confirm that both pericytes and endothelial cells are actively dividing. Because proliferative phase IHs are high-flow lesions, although typically without significant arteriovenous shunting, they often contain enlarged draining veins with thick, asymmetric walls.

Involuting IHs present different diagnostic challenges. Mitotic figures wane, and apoptotic bodies and masts...
cells increase in number during early involution. In Lesional capillaries begin to disappear. There is no evidence of thrombosis, and inflammation is not prominent. As involution proceeds, lesional capillary basement membranes become thick and hyalinized and contain specks of apoptotic debris (Fig 5). Eventually all that remains in an end-stage lesion is loose fibrous or fibrofatty stroma, containing a few residual “ghost” vessels composed of residual, thickened rinds of basement membrane material containing apoptotic debris and without intact cellular linings. Epidermal atrophy and underlying fibrous scar tissue may be present if the lesion ulcerated in the proliferative phase. Large arteries and veins modeled during the high-flow proliferative phase do not completely regress when the capillary bed drops out and thus are often present in involuting IH. This phenomenon, paired with loss of endothelial mitotic activity, may lead to mistaken histologic diagnosis as a vascular malformation. Misdiagnosis can usually be avoided by considering overall histologic appearance and clinical history. Ultimately, as discussed below, the issue can be resolved by GLUT1 immunoreaction, because involuting infantile IHs, but not malformations, will show GLUT1 immunopositivity in residual lesion-type capillaries. Histologic examination, accompanied by routine immunohistochemical studies, shows that proliferative phase infantile IHs are complex cellular mixtures with large complements of endothelial cells, pericytes, mast cells, and interstitial dendritic cells. Electron microscopy reveals plump endothelial cells lining small lumina and resting on a multilaminated basement membrane that envelops a cuff of pericytes. The endothelial cells of IH have been reported to immunoreact positively for “normal” endothelial markers of the blood vasculature, such as CD31, CD34, factor VIII–related antigen (von Willebrand factor), and others. Currently, the most useful and widely used immunohistochemical marker for the diagnosis of IH is GLUT1. GLUT1 is strongly expressed by endothelial cells of IHs at all stages of their evolution and is not expressed by other benign vascular anomalies and reactive proliferations. GLUT1 immunohistochemistry is frequently used to distinguish IHs from other vascular neoplasms and provides convincing evidence that IHs are indeed as biologically distinctive as they are clinically distinctive.

**FIGURE 5**
Involutive phase IH. Lesional capillaries are set within loose fibro-adipose tissue and are less densely packed than in the proliferative phase. Note the thickened and hyalinized basement membranes studded with apoptotic debris, reflective of the involutive process. Residual lining endothelial cells are mitotically inactive. (Photo courtesy of Paula North, MD)

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**Highlights of This Section**
- Proliferating IHs are well circumscribed and lack a capsule.
- Involuting IHs are fibrofatty and less defined.
- GLUT1 is a commonly used immunochemical marker for IH.

**CLINICAL PRESENTATION, COMPLICATIONS, AND ASSOCIATIONS**

**Phases of Growth**
IHs exhibit a characteristic life cycle. Clinical observations have suggested that there are at least 2 dynamic evolutionary phases, namely, proliferation and involution. Proliferation occurs during early infancy; gradual spontaneous involution or regression starts by 1 year of age. An intermediate period between proliferation and involution during mid-to-late infancy, often referred to as the “plateau” phase, more likely represents a period of temporary balance between individual cells that are proliferating and those undergoing involution and apoptosis. The process of involution takes several years and varies in duration.

**Proliferative Phase (Up to 12 Months of Age)**
Premonitory findings in the skin during early infancy may include localized blanching or localized macular telangiectatic erythema. As endothelial cell proliferation continues, the IH enlarges, becomes more elevated, and develops a rubbery consistency. During this period, IHs often show surrounding pallor and dilatation of surrounding veins. During rapid growth periods, ulceration may arise, leading to pain and eventual scarring.

IHs typically have their clinical onset before 4 weeks of age. They proliferate for variable periods of...
time, depending in part on their morphology and configuration. However, most IH growth appears to occur between 1 and 2 months of age.68 A large prospective study has indicated that 80% of IH size is generally reached by 3 months, and most growth is completed by around 5 months of age.66 Deep IHs appear somewhat later and grow somewhat longer than their superficial counterparts.66

**Involution Phase**

For most infants with IH, involution begins between 6 and 12 months of age. Although the process continues over years, the majority of tumor regression occurs before age 4.48,69,70 As IHs involute, most lesions flatten and shrink from the center outward. For those with a superficial component, this is accompanied by “central clearing” or graying of the surface. Although IHs generally undergo spontaneous regression, observations of “maximal involution” do not necessarily imply complete resolution. Indeed, approximately 50% to 70% of IHs resolve, leaving behind residual skin changes, including telangiectasia, fibrofatty tissue, redundant skin, anetoderma, dyspigmentation, or scar.71

**Highlights of This Section**

- IHs usually make their initial appearance before 4 weeks of age and complete most of their growth by 5 months of age.
- Involution of IHs begins as the child approaches 12 months of age. In most cases, the majority of involution is completed by age 4.

**Clinical Appearance**

During the proliferative phase, IHs can be classified on the basis of their soft tissue depth.61,62,72 Superficial IHs (Fig 6A) are those in which the surface of the tumor appears red and there is little to no discernible subcutaneous component; historically, these IHs have been described as being of the “strawberry” type. Deep IHs (Fig 6B) are those in which the tumor resides deep to the skin surface, and their subcutaneous location results in a bluish surface hue or no evident surface changes; historically, these have been referred to as “cavernous,” an imprecise term that is no longer commonly used. Combined, mixed, or compound IHs (Fig 6C) are those in which both superficial and deep components coexist. Superficial IHs tend to appear earlier and begin to involute sooner than their deep counterparts, which, by contrast, tend to arise later and grow for longer periods of time before involuting (on average, approximately 1 month more).62,64,66 Investigations into these differences confirm that these timelines represent characteristic growth patterns for these IHs rather than arising out of observational bias.66 As might be expected, those IHs with a mixed morphology have a growth pattern that is intermediate between those associated with superficial and deep IHs. These observations indicate that deep IHs require a longer period of monitoring than those with superficial morphology.

A specific subtype of superficial IH has been variably referred to as an abortive, nonproliferative, arrested-growth, minimal-growth, nascent, reticular, or telangiectatic IH.73–76 This type of IH presents as a macular, telangiectatic patch that may be accompanied by blanching of the involved skin (Fig 7). Unlike most IHs, abortive IHs lack an obvious significant proliferative phase. Approximately two-thirds of these lesions are situated on the lower extremities. Many are accompanied by localized, small papular regions of vascular tissue growth, often around the periphery.77 Abortive IHs share with more typical IHs characteristic surface markers (eg, GLUT1), confirming that they are true IHs; however, their growth phase may be arrested. Many of these telangiectatic IHs also involute more rapidly, sometimes before 1 year of age.78 Nevertheless, complications such as ulceration may occur. These IHs may also be segmental and occasionally have syndromic associations (see section entitled “IH Syndromes and Associations”).79
IHs may also be classified on the basis of their anatomic configuration as either localized (focal), segmental, indeterminate, or multifocal.\(^2^6,8^0,8^1\) Localized (focal) IHs are discrete lesions that seem to arise from a single focal point, whereas segmental lesions cover a territory that is presumed to be determined by embryonic neuroectodermal placodes.\(^8^2\) Segmental IHs tend to involve a larger surface area of skin. Segmental IHs of the face have been observed to conform to unique developmental units, which have been mapped into 4 distinct patterns: frontotemporal, maxillary, mandibular, and frontonasal (Fig 8).\(^8^2\) Lesions that are not definitively focal or segmental are considered indeterminate. Multifocal lesions are focal lesions occurring at more than 1 anatomic site. One large study found that most IHs (67.5%) are localized, whereas the remainder were segmental (13%), indeterminate (16.5%), or multifocal (3.6%).\(^8^3\)

The presence of a large, facial segmental IH is a hallmark sign of PHACE syndrome,\(^2^5\) whereas large segmental IHs of the anogenital and lumbosacral areas may be associated with genitourinary system and spinal cord anomalies as part of other syndromes\(^8^4\)–\(^8^6\) (see section entitled “IH Syndromes and Associations”). More recently, it has been recognized that extracutaneous manifestations may also arise in association with segmental IHs involving other anatomic sites, as part of the so-called PHACE-without-face phenomenon.\(^8^7\) These patients may have segmental IHs of the upper chest, shoulder, or arm in the absence of facial IH involvement and in conjunction with structural heart disease, aortic or other major vessel anomalies, central nervous system and sternal defects, or eye anomalies. Multifocal cutaneous IHs are frequently isolated to the skin but may also serve as markers for underlying hepatic involvement (Fig 9).\(^8^8\)–\(^9^1\) Previous retrospective reports\(^2^6,8^1\) suggested that the presence of a large or segmental (>5 cm) cutaneous IH might prove a useful marker for hepatic IHs. However, results from a large prospective study suggest that it is the number of cutaneous IHs rather than their size that is the more predictive factor.\(^9^2\) When 5 or more IHs are present on cutaneous examination, ultrasonography may be helpful in assessing potential hepatic involvement.\(^8^4,9^3\) Hepatomegaly and congestive heart failure also suggest the presence of liver IH.

Highlights of This Section

- IHs are characterized as superficial, deep, or mixed and as focal, multifocal, or segmental.
- Superficial IHs appear earlier and begin involution sooner than their deeper counterparts.
- Segmental IHs are more commonly involved in PHACE (see text for definition) and other IH syndromes and associations.
- The presence of more than 5 focal IHs suggests a higher risk of hepatic involvement.

FIGURE 7
Abortive IHs are macular, telangiectatic patches that have failed to fully proliferate.

FIGURE 8
(A) Patterns of segmental IH of the face extracted from image analysis: defined. Seg1 (frontotemporal), Seg2 (maxillary), Seg3 (mandibular), and Seg4 (frontonasal). (B) An ulcerated segmental IH in the maxillary distribution.

FIGURE 9
Multifocal cutaneous IHs in a child with IH of the liver.
Complications

Although most IHs do not require urgent treatment, a minority may develop function-threatening or life-threatening complications, necessitating therapeutic intervention. One study determined that approximately 24% of patients with IH who were referred to a group of tertiary care dermatology practices experienced some complication related to their IH.84 It is therefore prudent for pediatric providers to remain vigilant of possible complications and of risk factors that may herald future complications.

Ulceration accounts for the majority of IH complications; others include bleeding, visual impairment, auditory impairment, congestive heart failure, and airway obstruction.84 Gastrointestinal bleeding has been reported as a complication of segmental intestinal hemangiomatosis, in which the IH is typically situated in the distribution of the mesenteric arterial system.94

The single best predictor of complications and the need for therapeutic intervention for IH is morphologic subtype.84 Focal IHs have the potential to cause complications primarily by virtue of their location on or near vital structures, such as the eye (amblyopia, astigmatism), nose (anatomic distortion and cartilaginous destruction), ears (anatomic distortion and cartilaginous destruction), lips (anatomic distortion and ulceration), airway (obstruction), or anogenital region (ulceration). On the face, focal lesions are 3 times more common than segmental IHs.91 Segmental IHs are more frequently complicated by ulceration.84 A prospective cohort study in 1058 patients undertaken to identify clinical characteristics predicting complications and need for treatment found, after controlling for size, that segmental IHs were 11 times more likely than localized IHs to develop complications and 8 times more likely to receive treatment.84 Segmental lesions tend to have longer proliferative phases, some with significantly prolonged duration of growth as long as 10 to 44 months, and may therefore require significantly longer treatment durations.94

The size of the IH was also an important predictor of the need for treatment in the aforementioned cohort study, although this analysis did not appear to control for anatomic subtype.84 The mean size of complicated IHs was 37.3 cm², compared with 19.1 cm² for uncomplicated IHs. In addition, IHs that received treatment of any type had a mean size of 30.4 cm², which was 11.1 cm² larger than those that did not receive treatment. However, the mean size of segmental IHs is approximately 10 times that of localized IHs,56 suggesting that morphology may indeed be a more important indicator of potential complications.

Anatomic location was also a predictor of complications due to IH.84 Facial IHs were complicated 1.7 times more frequently than nonfacial IHs; they were also 3.3 times more likely than their nonfacial counterparts to receive some form of therapy, likely because of concerns for cosmesis. Periocular IHs and those in the “beard” distribution are also more likely to require intervention, as described below. In 1 study, perineal IHs were the most likely to ulcerate.95

Ulceration

Ulceration, or breakdown of the IH skin surface, occurs with an estimated incidence of 5% to 21%.96 Ulceration was the most common complication in a large prospective cohort of children with IHs, occurring in 16% of the study population.97 Ulceration can lead to significant pain, bleeding, and secondary infection. Ulceration also usually results in scarring, with the risk of permanent disfigurement. As a result, prompt initiation of therapy is essential in the management of ulcerating IHs.

The specific mechanisms resulting in IH ulceration are poorly understood. It has been hypothesized that ulceration may develop secondary to increased tissue hypoxia, which leads to the development of dermal fibrosis and then progresses to surface breakdown.98 In such cases, early white discoloration of an IH, possibly representing superficial dermal fibrosis, may be a premonitory sign of impending ulceration.99 Other proposed mechanisms include outgrowing of the blood supply or rapid expansion exceeding the elastic capabilities of the skin.95,100

Several studies have shown that certain subsets of patients with IHs are at higher risk of ulceration. As discussed previously, superficial and segmental IHs have been found to be at higher risk of ulcerating.96–98,101 In addition, specific locations at higher risk of ulceration include the head, neck, perioral, and perineal/perianal regions and intertriginous sites (Fig 10).96–98,102 The neck and anogenital regions sustain maceration and friction, which may contribute to the development of ulceration. Ulceration has also been noted to occur more frequently in infants younger than 4 months, a period of time during which the IH
is actively proliferating. See the section entitled "Management of Ulcerated IH" for a discussion in greater detail.

**Bleeding**

Although concern for potential bleeding in IH is common among caregivers and providers, it occurs rarely and almost exclusively in ulcerated lesions. The majority of bleeding that occurs in nonulcerated IHs is minor and easily controllable with pressure. The most common such scenario is an IH that has sustained minor surface trauma (ie, from friction or a fingernail), bled minimally, stopped bleeding spontaneously or with minimal sustained pressure, and subsequently presents with surface hemorrhagic crusting.

In a large prospective study of ulcerated IHs, bleeding occurred in 41% of lesions but was clinically significant in only 2% of these cases. Significant bleeding requiring blood transfusion or other intervention is infrequently reported. Rare instances of life-threatening bleeding have been observed, including 1 report of ulceration of a segmental neck IH into arterial vessels, the bleeding from which necessitated transfusions, systemic and topical treatment of the IH, embolization, and surgical excision.

**Feeding Impairment**

Feeding impairment can occur in infants with IHs involving either the perioral region or the airway. Infants with ulcerated lip IHs may be unable to latch onto a nipple secondary to severe pain, which can lead to impaired feeding. Obstructive airway IHs may complicate breathing and swallowing, also leading to impaired feeding. In a small case series in infants with complicated facial IHs, several with ulcerated perioral lesions or airway IHs had feeding and oral sensory problems that resulted in failure to thrive.

**Airway Involvement and Obstruction**

Airway IHs can occur in the presence or absence of skin findings. Symptomatic obstructive airway IHs, including supra- and subglottic IHs, usually present with progressive biphasic inspiratory and expiratory stridor during the first 6 to 12 weeks of age as the lesion is proliferating. Affected infants may also rapidly develop noisy breathing or a hoarse cry.

The cutaneous findings associated with underlying airway involvement, when present, help to identify those patients at greatest risk of airway IHs. Cutaneous IHs in a "beard" distribution, defined as involving the preauricular regions, chin, anterior neck, or lower lip (Fig 11), have been associated with airway involvement. Infants with IHs within this distribution bilaterally appear to be at an even higher risk of...
having associated airway involvement; in a recent series of 17 infants with airway IHs, bilateral involvement of the lower facial segment was present in 13 (76%). Early referral to otolaryngology of infants with severe stridor and a cutaneous IH in the "beard" distribution is advisable, because airway involvement can be life-threatening if diagnosis and treatment are delayed. In less symptomatic children, a high kilovoltage radiograph of the airway may be useful in identifying subglottic IH. Airway IHs are discussed in greater detail in the subsection under "IHs With Special Anatomic Concerns" entitled "Airway."

Visual Impairment and Other Ocular Complications

IHs occurring within the orbit have the potential to cause mechanical ptosis, strabismus, anisometropia, or astigmatism, which can quickly lead to the development of amblyopia. Studies have identified specific characteristics of periocular IHs, which place the child at higher risk of amblyopia. These include periocular IHs that are larger than 1 cm in diameter, nasal location of the IH, associated ptosis, eyelid margin change, or displacement of the globe. Orbital IHs are discussed in greater detail in the subsection entitled "Eye and Orbit" under "IHs With Special Anatomic Concerns."

Congestive Heart Failure and Hypothyroidism

Although rare, high-output congestive heart failure can occur in infants with large IHs as a result of arteriovenous shunting of a large blood volume through the lesion. This complication has been reported in infants with large cutaneous IHs and RICHs and in those with diffuse or multifocal hepatic IHs. Symptomatic infants may present with difficulty feeding, poor growth, heart murmur, or hepatomegaly. The cardiac compromise usually improves with treatment of both the heart failure and the IH.

Diffuse lesions of the liver may also be associated with severe consumptive hypothyroidism caused by excess production of type 3 iodothyronine deiodinase. Liver IHs are discussed in greater detail in the subsection entitled "Liver" of "IHs With Special Anatomic Concerns."

IH Syndromes and Associations

A small subset of children with IH will exhibit associated congenital anomalies. The best-known such association is PHACE (Online Mendelian Inheritance in Man 606519). The disorder is also referred to as PHACES to include potential ventral midline defects, specifically Sternal cleft and/ or Supraumbilical raphe. Originally described as a "syndrome," PHACE is more appropriately termed an association, although there are recent data suggesting that chromosomal region 7q35 may provide a genetic susceptibility to exhibit the PHACE phenotype.

The spectrum of anomalies in PHACE syndrome and the ipsilateral relationship between such anomalies and cutaneous IH strongly suggest a "developmental field defect," whereby an insult at a critical time in embryogenesis gives rise to similar developmental outcomes. The precise timing of such an insult in PHACE syndrome is speculative, but both the anatomic IH patterns and several of the associated structural abnormalities point to changes early during the first trimester, probably within the first 3 to 12 weeks of gestation before or during early vasculogenesis. PHACE syndrome is now understood to be predominantly a congenital vasculopathy. In fact, many of its features can be explained as downstream events of arteriopathy with resultant ischemia, and it has been hypothesized that vascular dysplasia may be a key or even primary event in the pathogenesis of PHACE syndrome.

Consensus criteria were recently developed for the diagnosis of PHACE syndrome (Tables 2 and 3). Clinical examination of the skin and eyes as well as detailed imaging of the head, neck, and chest are required to make the diagnosis. More than 90% of infants with PHACE syndrome exhibit more than 1 extracutaneous anomaly, although very few manifest the complete spectrum. In contrast to nonsyndromic IH, PHACE syndrome...
is more common in full-term singleton infants of normal birth weight, although females are still more commonly affected.120

The hallmark of PHACE syndrome is a large, segmental, often superficial IH, characteristically located on the face, scalp, and/or neck (Fig 12). PHACE syndrome-associated IHs most commonly affect facial segments 1 and/or 3, which also confers a particularly high risk of associated central nervous system involvement.84,119

PHACE syndrome is not exceedingly rare, and probably even more common than Sturge-Weber syndrome.121 The segmental IH associated with PHACE is sometimes confused with the port wine stain associated with Sturge-Weber syndrome, especially in the newborn period before significant IH proliferation or in cases of “minimal growth” IH in which there is an absence of significant proliferation. The risk of PHACE syndrome in an infant presenting with a large, segmental IH ($\geq 22 \text{ cm}^2$) of the head or neck is approximately one-third.120

Cerebrovascular anomalies, present in more than 90% of patients, are the most common extracutaneous feature of PHACE syndrome, followed by cardiac anomalies (67%) and structural brain anomalies (52%).84 The most common arterial abnormality in PHACE syndrome is dysgenesis of the anterior circulation, particularly within the internal carotid artery.119 The neuroanatomic and cerebrovascular anomalies observed in PHACE may lead to a number of neurologic sequelae, including motor and speech delays, seizures, migraine-like headaches, and rarely, arterial ischemic stroke.121 Hearing loss (conductive or sensorineural) has also been reported in PHACE syndrome, particularly when the IH involves the ear and periauricular scalp, which can be related to the presence of ipsilateral

| TABLE 2 Consensus Algorithm for the Diagnosis of PHACE Syndrome |
|-----------------------|-----------------------|-----------------------|-----------------------|
| PHACE Syndrome         | Possible PHACE Syndrome |
| Facial hemangioma >5 cm in diameter plus 1 major criterion or 2 minor criteria | Facial hemangioma >5 cm in diameter plus 1 minor criterion | Hemangioma of the neck or upper torso plus 1 major criterion or 2 minor criteria | No hemangioma plus 2 major criteria |

Adapted from ref 25.

| TABLE 3 Consensus Diagnostic Criteria for PHACE Syndrome |
|-----------------------|-----------------------|-----------------------|
| Organ System          | Major Criteria        | Minor Criteria        |
| Cerebrovascular        | Anomaly of major cerebral arteries | Persistent embryonic artery other than trigeminal artery |
| | Dysplasia of the large cerebral arteries | Proatlantal intersegmental artery (types 1 and 2) |
| | Arterial stenosis or occlusion with or without moyamoya collaterals | Primitive hypoglossal artery |
| | Absence or moderate-severe hypoplasia of the large cerebral arteries | Primitive otic artery |
| | Aberrant origin or course of the large cerebral arteries | Persistent trigeminal artery |
| | Persistent aneurysms of any cerebral arteries | Saccular aneurysms of any cerebral arteries |
| Structural brain       | Posterior fossa anomaly | Enhancing extraaxial lesion with features consistent with intracranial hemangioma |
| | Dandy-Walker complex or unilateral/bilateral cerebellar hypoplasia/dysplasia | Midline anomaly |
| | | Neuronal migration disorder |
| Cardiovascular         | Aortic arch anomaly | Ventricular septal defect |
| | Coarctation of aorta | Right aortic arch (double aortic arch) |
| | Dysplasia | |
| | Aneurysm | |
| | Aberrant origin of the subclavian artery with or without a vascular ring | |
| Ocular                 | Posterior segment abnormality | Anterior segment abnormality |
| | Persistent hyperplastic primary vitreous | Microphthalmia |
| | Persistent fetal vasculature | Sclerocornea |
| | Retinal vascular anomalies | Coloboma |
| | Morning glory disc anomaly | Cataracts |
| | Optic nerve hypoplasia | |
| | Coloboma | |
| | Peripapillary staphyloma | |

Adapted from ref 25.

a Includes kinking, looping, tortuosity, and/or dolichoectasia.

b Internal carotid artery, middle cerebral artery, anterior cerebral artery, posterior cerebral artery, or vertebrobasilar system.

c Callosal agenesis or dysgenesis, septum pellucidum agenesis, pituitary malformation, or pituitary ectopia.

d Polymicrogyria, cortical dysplasia, or gray matter heterotopia.
intracranial IH involving auditory structures. It has been suggested that children with PHACE syndrome and periauricular IH be evaluated with both MRI and audiometric testing.\textsuperscript{122}

Cardiovascular anomalies are the second most common extracutaneous manifestation of PHACE syndrome. The aortic coarctation observed differs from classic coarctation in that it occurs in a more proximal location, often involves the arteries feeding the upper extremities, and affects longer segments, which may preclude detection based on a blood pressure gradient between the upper and lower extremities. The aortic anomalies in PHACE syndrome are often noted to be particularly unusual and severe, often requiring surgical repair; thus, detailed imaging of the arch is essential.\textsuperscript{123}

Even in asymptomatic infants, MRI or magnetic resonance angiography (MRA) of the head and neck is indicated, especially given the known potential for progressive vasculopathy and resultant ischemic events in a small subset of severely affected patients.\textsuperscript{124} Arterial ischemic stroke, a rare but devastating complication, appears to be more likely in patients with PHACE who exhibit significant narrowing or nonvisualization of large cerebral arteries, especially when more than 1 vessel is involved and/or if there are associated cardiovascular morbidities such as coarctation of the aorta.\textsuperscript{125}

Through serial neuroimaging of high-risk infants, progressive cerebrovascular changes may be identified early, and neurosurgical revascularization procedures can be performed to potentially reduce arterial ischemic stroke–related morbidity and mortality.\textsuperscript{125} The presence of severe cerebrovascular and/or cardiovascular arterial anomalies in patients with PHACE syndrome may preclude the use of propranolol for treatment of IH in this population, or require dose modification. (see section entitled “Medical Therapy for IH”).

LUMBAR syndrome (Lower body IH and other cutaneous defects, Urogenital anomalies and ulceration, Myelopathy, Bony deformities, Anorectal malformations and arterial anomalies, and Renal anomalies) may be best considered the “lower half of the body” variant of PHACE syndrome.\textsuperscript{85} LUMBAR has also been previously described under the competing acronyms SACRAL\textsuperscript{97} (Spinal dysraphism, Anogenital anomalies, Cutaneous anomalies, Renal and urologic anomalies, associated with Angioma of Lumbosacral localization) and PELVIS\textsuperscript{86} (Perineal hemangioma, External genitalia malformations, Lipomyelomeningocele, Vesicorenal abnormalities, Imperforate anus, Skin tag). The IHs are usually segmental lumbosacral or anogenital lesions. In an analysis of 24 new patients and a review of 29 published cases, IHs in association with LUMBAR were noted to be segmental and often “minimal growth” in morphology.\textsuperscript{85} Such IHs were often extensive (eg, involving the entire leg) and showed additional potential for ulceration and, rarely, underdevelopment of the affected limb. Like PHACE syndrome, the cutaneous IHs and underlying anomalies showed regional correlation. Myelopathies, particularly spinal dysraphism, were the most common extracutaneous anomaly. Interestingly, arterial anomalies were noted in a minority of patients who were specifically studied for such anomalies, although the true incidence and long-term risks are unknown. Imaging is region-specific; MRI is useful in delineating the extent of lumbosacral involvement and potential myelopathy, whereas additional imaging with MRA may be warranted for infants with extensive lower limb involvement to assess for arterial anomalies.

**FIGURE 12**

A. Frontotemporal segmental IH typical of PHACE syndrome. B, Sternal clefting characteristic of PHACE syndrome (scar is congenital, not surgical).

**Highlights of This Section**

- PHACE syndrome includes features of Posterior fossa defects, Hemangiomas, cerebrovascular Arterial anomalies, Cardiovascular anomalies including coarctation of the aorta, and Eye anomalies.
- The hallmark of PHACE syndrome is a large, segmental IH, characteristically located on the face, scalp, and/or neck.
- The most common extracutaneous features of PHACE syndrome are cerebrovascular anomalies, followed by cardiac anomalies and structural brain anomalies.
- LUMBAR syndrome may be best considered the “lower half of the body” variant of PHACE syndrome and may be associated with urogenital, anal, skeletal, and spinal cord anomalies.
IMAGING OF IH

The diagnosis of IH is generally made on the basis of history and clinical appearance. Occasionally, imaging of the lesion may be required when the diagnosis is uncertain, when evaluation of extent is necessary, or when response to therapy needs to be monitored. IH-associated anomalies, such as spinal dysraphism, anogenitourinary anomalies, and PHACE syndrome, are also best imaged with MRI. However, the risk of early exposure to anesthesia is a consideration in determining the urgency and type of imaging for IH.

Ultrasonography is a reasonable initial imaging modality for diagnosing IH, because it is inexpensive and does not require sedation. The sonogram generally reveals a well-defined high-flow parenchymal mass with possible shunting. During the involution phase, areas of increased echogenicity (fat replacement) can be seen within the lesions. Gray scale and color Doppler ultrasonography have also demonstrated utility in monitoring the response of IH to medical therapy. Ultrasonography is also a good first-line modality to screen patients with multifocal IHs for liver or visceral involvement, although MRI is preferable to assess complicated or extensive visceral lesions. The extent of the lesion and the surrounding anatomy are better shown on MRI. The most useful sequences include T1-weighted images with and without fat saturation, T1-weighted images with fat saturation post-gadolinium administration, T2-weighted images with fat saturation, and flow-sensitive sequences such as gradient echo or MRA. Proliferating IHs typically appear as well-defined masses with features of high flow and intermediate signal intensity on T1-weighted images and high signal intensity on T2-weighted images. Flow voids may be apparent on T2-weighted and flow-sensitive sequences, along with high-flow feeding arteries and draining veins. With administration of intravenous gadolinium, lesion enhancement is usually early, with intense and uniform enhancement on delayed images; however, diffuse or multifocal hepatic lesions may show early enhancement peripherally and delayed filling centrally (centripetal enhancement). Nonenhancing regions may represent thrombosis or necrosis. During the involution phase, as deposits of fat replace the lesion, foci of increased signal can be seen on T1-weighted images, and postcontrast images reveal less avid enhancement.

Computed tomography (CT) is mentioned only because it is occasionally ordered when a diagnosis of IH is not expected. CT findings are similar to those on MRI, including well-defined and avidly enhancing lesions during the proliferating phase and less pronounced enhancement during the involution phase. Although these studies are shorter in duration than MRI (reducing the likelihood that general anesthesia will be necessary), CT carries the disadvantage of exposing young children to ionizing radiation and its attendant risks.

CLINICAL APPROACH TO IH

The traditional clinical approach to IH has been one of “benign neglect.” The observation that, as a neoplasm, IH has the unique ability to undergo involution has led many practitioners to believe that the best management is to “leave it alone and it will go away.” However, 1 study from a group of referral pediatric dermatology practices suggests that more than one-third of patients with IH require some sort of intervention. Hence, although this number may reflect referral bias, it is clear that some IHs are associated with a high risk of complications or permanent disfigurement. In many such cases, early intervention may be justified to potentially arrest the growth of the lesion, reduce associated complications, and avoid years of psychosocial concerns.

The first consideration in the management of IH is whether intervention is necessary. The indications for intervention include the following: (1) emergency treatment of potentially life-threatening complications; (2) urgent treatment of existing or imminent functional impairment, pain, or bleeding; (3) evaluation to identify structural anomalies potentially associated with IH; and (4) elective treatment to reduce the likelihood of long-term or permanent disfigurement. Life-threatening lesions include obstructing IHs of the airway as well as liver IHs associated with high-output congestive heart failure and severe hypothyroidism. Pain and bleeding are examples of urgent sequelae that occur as a result of ulceration; affected children may have failure to thrive as well. Other examples of functional impairment include ocular impairment (loss of visual axis leading to deprivation amblyopia, astigmatism,
strabismus, visual field cuts), impaired feeding because of involvement of the lips or mouth, and reduced mobility because of complicated involvement of the extremities. Structural anomalies of concern include spinal dysraphism associated with lumbosacral IHs as well as anomalies associated with PHACE and other IH “syndromes.” Long-term and permanent disfigurement is a concern with IHs of certain anatomic sites (eyelid, nasal tip, lip, breast, genitalia) and with severe ulceration, because these will ultimately leave a scar of similar size.

Most IHs are uncomplicated and are not likely to fall into any of these categories (Fig 13); the practice of initial observation or “watchful waiting” is reasonable for such lesions. However, because the clinical presentation of IH can change within days, it is prudent for pediatric providers to reexamine frequently, as often as weekly, those children with lesions at high risk of causing functional or cosmetically critical changes, because many uncomplicated lesions may become complicated ones in early infancy. For less concerning IHs, providers may wish to counsel the family regarding changes of importance, such as rapid growth or ulceration, and to establish with the family a means to see the child on short notice if such changes are observed.

Central to the decision of whether to intervene is a discussion of the risks, benefits, and alternatives associated with each of these choices and with each potential intervention. Proper informed consent from the family is paramount in achieving a successful and satisfying physician-patient relationship as well as a good therapeutic result. Once a decision has been made to intervene, the second consideration is which therapeutic modalities are most appropriate. There is no formula or algorithm that easily addresses all of the factors in this decision; as a result, the treatment plan is customized for each patient. Relevant factors include age and medical condition of the patient; growth phase, location, and size of the lesion or lesions; degree of skin involvement; severity of complication and urgency of intervention; potential for adverse psychosocial consequences; parental preference; and clinician experience. A Cochrane review found a dearth of well-designed clinical trials on which appropriate interventions for IH could be determined.

Whether IH affects the psychosocial well-being of affected patients, and the age at which it may do so, is uncertain. Some authors suggest that “children first represent and reflect on themselves as independent, objective entities” in the latter half of the second year of life and that the emotional responses of others may affect a child’s mood even earlier than 12 months of age. Thus, there may be some effect on the child even before entering preschool. In contrast, a review of the existing literature on psychosocial ramifications of IH was less concerning. Among the 7 studies cited, questionnaires that were validated but not specific for IH revealed few or no signs of psychosocial impact in children with IHs. The authors did note that the studies were conducted in small groups of parents, and all were flawed in one way or another. In a small study, quality of life among children 5 to 8
years of age who had IHs of the head and neck measuring 2 cm or greater was compared with that of normal controls. Although the questionnaires were not disease-specific, the authors found no differences in quality-of-life indices or in self-perception scores. Further complicating this subject is the fact that quality-of-life investigations in young children require proxy reporting that often reflects quality of life as perceived by the proxy rather than the child. Thus, no definitive statement can be made regarding psychosocial ramifications of IH; however, many clinicians who specialize in the field will consider treatment of those IHs projected to be cosmetically significant beyond 4 years of age.

Details related to IH stage have been addressed in a study examining growth characteristics of IHs. The largest increase in IH size occurred at a mean age of 3 months, and by 5 months of age both segmental and localized IHs had reached 80% of their final size. As a result, therapy initiated after the early proliferative phase is less likely to be effective in controlling the growth of the lesion or in prevention of complications. Age and stage are also factors in the effectiveness of pharmacotherapy for IH. Early experience with systemic steroids for IH suggested that younger children had a better response to therapy, and most studies of their mechanism of action suggest they inhibit components of the proliferative process. Similar data for propranolol therapy are not yet available, but proposed mechanisms of its action also suggest primary activity during proliferation. Conversely, recent retrospective studies indicate that β-blocker therapy for IH can be effective beyond the proliferative phase as well.

Age and growth phase are also considerations when surgery for IH is being considered. For example, in patients who have undergone early surgery and in whom residual IH intentionally or inadvertently remains postoperatively, there is potential for additional growth of the lesion after the procedure. In addition, because IHs are benign lesions with the potential to involute, surgeons do not always endeavor to obtain disease-free margins, instead allowing involution to assist in achieving the final result. On occasion, in surgery for well-involved IHs, tissue may even be left behind intentionally, using the fibrofatty remnant to serve as filler to preserve normal tissue contours. Lesion-related factors, such as location, size, and degree of skin involvement or ulceration, often dictate the feasibility of a given treatment modality. For example, a pedunculated eyelid lesion causing ptosis or ectropion or a small, ulcerated lesion that is certain to scar may lend itself better to early surgical excision rather than medical therapy. Conversely, an extensively ulcerated segmental IH or a lesion of the genitalia is more appropriately addressed with medical therapy.

Parental preference is another critical factor in treatment selection, more so in elective cases than in those that are emergencies or urgent cases. Parents will often have strong feelings, particularly about surgical intervention or systemic medical therapy, that will have a major effect on treatment planning for the child. Similarly, the choice of treatment may be influenced by the experience of the treating provider and his or her familiarity with the diversity of potential interventions. For these reasons, it may be preferable for complicated IHs to be managed by a practitioner or team who has experience with all of the available therapeutic options.

### Highlights of This Section

- The indications for intervention for IH include the following:
  1. emergency treatment of potentially life-threatening complications;
  2. urgent treatment of existing or imminent functional impairment, pain, or bleeding;
  3. evaluation to identify structural anomalies potentially associated with IH; and
  4. elective treatment to reduce the likelihood of long-term or permanent disfigurement.

- There is no algorithm to determine the most appropriate intervention for IH. Factors affecting this choice include the following:
  1. age of the patient,
  2. growth phase of the lesion,
  3. location and size of the lesion,
  4. degree of skin involvement,
  5. severity of complication and urgency of intervention,
  6. potential for adverse psychosocial consequences,
  7. parental preference, and
  8. physician experience.

### MANAGEMENT OF ULCERATED IHs

The management of ulcerated IHs includes attention to wound care, pain, and IH growth. Unfortunately, there are no high-quality studies to guide care of the ulcer, and therefore treatment preferences are often based on case experience.
Approaches to ulcerated IHs are summarized in Table 4.

Some clinicians liken the management of ulceration to that of superficial burns and suggest culture and diligent wound care. In 1 study, 16% of ulcerated IHs were considered to be infected on clinical grounds, and cultures revealed pathogens in half of these cases. Reepithelialization may be facilitated by debriding crusts with the use of warm compresses. The ulcer is then covered with a barrier to prevent excessive drying, control pain, reduce the risk of trauma and potential bleeding, and reduce the risk of bacterial colonization or infection. Such treatments may consist of topical antibiotics or anesthetics, wound dressings, barrier creams, or all of the above. Most ulcerations improve with this conservative approach to wound care.

Because ulceration is usually associated with proliferation of the IH, therapies to curb its growth are often used. Several case series have reported successful treatment of IH ulceration with propranolol therapy. Topical timolol has been reported to be successful for ulceration, but its absorption is unpredictable in this setting. Systemic steroids may also be a reasonable alternative.

In refractory cases, pulsed-dye laser (PDL) therapy may also be effective in managing ulcerated IHs. In a prospective study in 78 children, 91% of the patients responded to laser therapy with a mean number of 2.0 treatments. Thus, PDL therapy may also be effective in managing ulcerated IHs, with oral prednisone for enlarging IHs. All 7 consecutive children with oral prednisolone for enlarging IHs. All 7 experienced cessation of lesional growth and no rebound growth after treatment. On the basis of this result, Fost and Esterly treated 6 children with oral prednisone for extensive IHs. All but 1 had dramatic regression after only 2 weeks of therapy. Subsequent studies have continued to show efficacy, although physicians have raised concerns about potential

### Highlights of This Section

- Management of ulcerated IH consists primarily of the following:
  1. barrier dressings,
  2. pain control, and
  3. control of IH growth.
- Adjuvant therapies may include the following:
  1. topical agents, including antibiotics, anesthetics, or wound dressings, and
  2. pulsed dye laser.

#### TABLE 4 Treatment Options in the Management of Ulcerated IH

<table>
<thead>
<tr>
<th>Wound Care</th>
<th>Adjuvant Therapies</th>
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<td><strong>Dressings</strong></td>
<td><strong>Antimicrobials</strong></td>
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<tr>
<td>White petrolatum–impregnated gauze</td>
<td>Metronidazole gel</td>
</tr>
<tr>
<td>Nonadherent dressings (eg, Mepitex</td>
<td>Mupirocin, gentamicin, bacitracin ointment</td>
</tr>
<tr>
<td>[(Mölnlycke Health Care; Gothenburg, Sweden), Teifal</td>
<td>Pain control</td>
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<td>Hydrocolloid dressings (eg, DuoDERM</td>
<td>Anesthetics (eg, lidocaine, benzocaine)</td>
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<td>{Convatec, Luxembourg})</td>
<td>Oral</td>
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<td><strong>Topical agents</strong></td>
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<tr>
<td><strong>Oral propranolol or steroids</strong></td>
<td>Early excision</td>
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</tbody>
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Adapted from ref 368.

#### MEDICAL THERAPY FOR IH

**Background**

Medical therapy for IH includes both topical and systemic administration of medications. Topical agents may be a consideration for smaller, more superficial IHs or those for which systemic therapy is contraindicated. Systemic therapy is usually initiated for large IHs, those with a high risk of functional impairment or disfigurement, and those refractory to other initial therapies. Beginning in the 1960s, systemic and intralesional steroids were the cornerstone of medical therapy for IH. Shrinkage of IH with systemic corticosteroid therapy was first observed serendipitously among patients with hemangioendotheliomas (KMP) treated for thrombocytopenia in the late 1950s and early 1960s. In 1967, Zarem and Edgerton treated 7 consecutive children with oral prednisolone for enlarging IHs. All 7 experienced cessation of lesional growth and no rebound growth after treatment. On the basis of this result, Fost and Esterly treated 6 children with oral prednisone for extensive IHs. All but 1 had dramatic regression after only 2 weeks of therapy. Subsequent studies have continued to show efficacy, although physicians have raised concerns about potential...
adverse effects of steroids administered in large doses for long periods of time.

In the late 1980s and early 1990s, interferon-α showed some promise in the treatment of steroid-resistant IHs. This drug is a cytokine produced by leukocytes that play a role in the innate immune response against viruses. When synthetic interferon-α2a was used to treat patients with HIV, an improvement in their Kaposi sarcoma lesions was noted.154 Because interferon-induced genes are upregulated during involution of IH, there was a theoretical basis for its mechanism of action in IH,152 and anecdotal reports as well as clinical trials subsequently documented its efficacy in vascular lesions, including IHs refractory to corticosteroid therapy.156,157 However, it is now clear that significant neurologic toxicities, including impairment of higher cortical and motor function, can occur and generally preclude its use as a first-line therapy.

In 2008, Léauté-Labrèze et al158 reported their serendipitous observation that oral propranolol, a nonselective blocker of β-adrenergic receptors used for decades to treat cardiac disorders in children, is effective and well tolerated in the management of IH. A year later, they reported their experience with 32 infants with severe IH who were treated with propranolol at 2 to 3 mg/kg per day in 2 to 3 divided doses.159 These infants responded well with a rapid, consistent, therapeutic effect and minimal adverse effects. Since that time, there have been numerous additional reports of the safe and effective use of propranolol for the treatment of medically complex as well as cosmetically significant IHs.160

### β-Adrenergic Blockers

For most clinicians treating complicated IHs, propranolol has become the first-line medical therapy; however, optimal dosing, treatment timing and duration, and risk of complications have not yet been established in randomized trials, and recommendations for monitoring are still evolving.161 An oral formulation free of alcohol, sugar, and paraben developed for use in children (Hemangeol; Pierre Fabre, Castres, France) received approval from the US Food and Drug Administration in March 2014. There is a paucity of data regarding other β-adrenergic blockers.162

**Mode of Action in IH**

The mode of action of propranolol in the treatment of IH is unknown. Proposed mechanisms include vasoconstriction, inhibition of angiogenesis (via suppression of VEGF-A and downregulation of MMPs and interleukin [IL] 6), regulation of the renin-angiotensin system, and inhibition of nitric oxide production; propranolol’s ability to stimulate apoptosis is equivocal.44,49,140,141,159,161,163–167 Investigators have shown the presence of β2-adrenergic receptors on capillary endothelial cells in proliferating IH, and vascular endothelial cell growth factors, which are elevated in rapidly growing IHs, are suppressed in the presence of β-adrenergic receptor blockade.158–160,168 It has also been suggested that propranolol may prevent the differentiation of IH stem cells into endothelial cells or pericytes,169 reduce contractility of pericytes,170 and/or promote adipogenesis.140,165,171

**Efficacy**

In a randomized controlled trial of oral propranolol in 460 infants aged 1 to 5 months with IH, patients administered a dose of 3.4 mg/kg per day exhibited a 60% rate of successful treatment (complete or nearly complete resolution of the target hemangioma), compared with a 4% rate among those treated with placebo.172 Another randomized trial in 40 patients found a marked improvement in IH volume, redness, and elevation among those taking propranolol compared with those taking placebo.173 In a 2011 comprehensive review of the literature, response to propranolol therapy was evaluated in 79 articles but quantified in only 6.160 Positive responses in all treated patients were reported in 86% of publications; the remaining 14% discussed at least some treatment failures. In total, 19 of 1175 patients in these publications were reported as treatment failures, suggesting a 1.6% treatment failure rate.160 Moreover, lightening of the color and softening of the tumor was noted in most children within hours to days of the initial dose of propranolol.158,159,173,174 After initiation of propranolol therapy, progressive improvement has been noted for at least 3 months in most patients.158,159,173,174 Like systemic corticosteroids, propranolol appears to stabilize IHs in their growth phase; however, it may also be effective after proliferation has ended. In 1 study that assigned visual analog scores to IHs in children treated with propranolol at ages 7 to 120 months, more than half of the patients achieved a greater rate of improvement in their scores after starting the medication.143 Other authors have also reported similar observations.142,175

**Pretreatment Assessment, Contraindications, and Risks of Therapy**

A complete history and physical examination, with special attention to the cardiac and pulmonary systems, aid in assessing a child’s candidacy for propranolol initiation. Electrocardiography is often ordered as well, particularly in younger infants, those with a low heart rate, and those with an examination or
family history consistent with congenital heart disease. Some clinicians also prefer to have a cardiology consultation before starting the medication. However, pretreatment cardiac screening appears to be of limited value in patients with an unremarkable cardiac history and examination. Relative contraindications to the use of propranolol for IH include cardiogenic shock, sinus bradycardia, hypotension, heart block greater than the first degree, heart failure, bronchial asthma, and known hypersensitivity to the drug (Table 5). Special precautions have been suggested for children diagnosed with PHACE syndrome and significant intracranial vascular anomalies because of the theoretically increased risk of acute ischemic stroke.

Experience in the management of hundreds of infants with IH has shown propranolol to have an excellent safety profile and high tolerability. The most commonly reported adverse effects of propranolol are sleep disturbance and coolness and mottling of the distal extremities. The use of β-blockers can be also be associated with adverse cardiac effects, including bradycardia and hypotension, both of which are generally asymptomatic and do not require intervention. Less common complications include bronchospasm and hypoglycemia, the latter of which has the potential to induce seizures. In a systematic review of propranolol treatment of IH, there were 371 total adverse effects reported in 1189 patients. Those most commonly reported were sleep disturbance (136 patients), acrocyanosis (61 patients), hypotension (39 patients, including 5 considered “symptomatic”), bradycardia (8 patients, including 1 considered symptomatic), and respiratory events including infections, wheezing, and stridor (35 patients).

Table 5 Contraindications and Potential Complications Associated With Propranolol Therapy

<table>
<thead>
<tr>
<th>Contraindications</th>
<th>Complications</th>
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<tbody>
<tr>
<td>Sinus bradycardia</td>
<td>Sinus bradycardia</td>
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<tr>
<td>Hypotension</td>
<td>Hypotension</td>
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<tr>
<td>Greater than</td>
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<tr>
<td>first-degree</td>
<td>Cool extremities</td>
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<tr>
<td>heart block</td>
<td>Sleep disturbance</td>
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<tr>
<td>Heart failure</td>
<td>Reactive airways</td>
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<tr>
<td>Cardiogenic shock</td>
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<tr>
<td>Reactive airways</td>
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<td>Hypoglycemia</td>
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<tr>
<td>Hypersensitivity</td>
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<td>to propranolol</td>
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<tr>
<td>hydrochloride</td>
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</table>

Adapted from ref 161.

Initiation of Therapy and Dosing

Although the optimal setting for the initiation of propranolol has yet to be established, a consensus group has suggested that inpatient hospitalization be considered for infants 8 weeks of age or younger, preterm infants less than 48 weeks’ postconceptional age, those with poor social support, and those with cardiac or pulmonary risk factors. Special precautions have been suggested for children diagnosed with PHACE syndrome and significant intracranial vascular anomalies because of the theoretically increased risk of acute ischemic stroke.

The group recommended initiating therapy at a dose of 1 mg/kg per day, with escalation to a target dose of 1 to 3 mg/kg per day, although this recommendation was made prior to the FDA approval of Hemangeol, which is dosed maximally at 3.4 mg/kg per day. The optimal dose for maintenance has yet to be established. The group’s recommended dosing frequency was 3 times daily; however, the drug has also been dosed twice daily and showed both safety and efficacy. Because the peak effect of oral propranolol on heart rate and blood pressure is 1 to 3 hours after administration, the group suggested that these measurements be taken at baseline, 1 and 2 hours after the first dose, and 1 and 2 hours after each dosage increase of ≥0.5 mg/kg per day. Heart rates or blood pressure measurements lower than 2 SDs from the mean suggest the need for cardiologic evaluation. It should be noted that, where there was controversy, the group recommended the most conservative approach to propranolol initiation.

The risk of hypoglycemia may be reduced by administering propranolol and feeding children at intervals not to exceed 8 hours (or 6 hours in younger infants). Children with any acute illness, especially one interfering with normal oral intake or one associated with vomiting or diarrhea, will require close monitoring and often a temporary decrease in dosing or cessation of therapy.

Duration of Therapy

The most dramatic improvement using propranolol for IH occurs within 3 to 4 months of initiation of therapy. However, many investigators continue therapy until patients reach an age when IH would normally begin to regress without treatment. Hence, treatment is often continued until at least 8 to 12 months of age, which, in most studies, equated to 3 to 12 months of therapy. For discontinuation of therapy, most practitioners taper propranolol gradually over a period of 1 to 3 weeks, primarily in an effort to prevent rebound sinus tachycardia. Rebound growth of IH has been observed in 6% to 25% of children, often well after their first birthday, leading some clinicians to wean propranolol over weeks to months. Rebound growth may be more likely in patients whose IH exhibited a long proliferative stage and a large subcutaneous component. In such cases, reintiation of therapy for variable periods of time may be necessary.
Topical \(\beta\)-Adrenergic Blockers

Several investigators have reported success using topical \(\beta\)-blockers in the treatment of IH. Timolol maleate is a nonselective \(\beta\)-adrenergic receptor inhibitor available in a concentration of 0.25% and 0.5%, which has been used by pediatric ophthalmologists in the United States for more than 30 years as a first-line therapy in children with glaucoma. In recent years, an extended-release gel-forming solution has become available in concentrations of 0.25% and 0.5%. Systemic absorption of the gel-forming solution is significantly lower than that of the solution, and absorption through intact skin is likely much less than that through the conjunctivae and lacrimal duct.190

Case reports and case series have shown a good response of IH to twice-daily topical application of timolol.191-195 In a randomized controlled trial, timolol was more effective than placebo in reducing the size and color intensity of small superficial IHs.196 Laboratory studies were not monitored in the majority of studies, and only 1 infant in 1 large series developed a transient sleep disturbance. Responses were best in patients who had superficial IHs, used the 0.5% gel-forming solution, and applied the medication for more than 3 months.195 Many experts now consider topical timolol gel-forming solution a reasonable consideration for uncomplicated, superficial IHs for which treatment is desired but the risk-to-benefit ratio is too great to justify systemic \(\beta\)-blocker therapy. However, there are valid concerns regarding the bioavailability of the drug when used topically in neonates and infants, especially in the treatment of larger or ulcerated lesions and those on or near mucous membranes.190

**Highlights of This Section**

- Propranolol, administered orally at a dose of 1 to 3.4 mg/kg per day, is efficacious in reducing the size and color intensity of IH.
- The mechanism of propranolol’s effect on IH likely involves several processes, including vasoconstriction, inhibition of angiogenesis, and stimulation of apoptosis.
- Common side effects of propranolol include sleep disturbance and discoloration with cooling of the hands and feet.
- Contraindications to the use of propranolol for IH include cardiogenic shock, sinus bradycardia, hypotension, heart block greater than first-degree, heart failure, bronchial asthma, and known hypersensitivity to the drug.
- A consensus report suggests that heart rate and blood pressure be determined at baseline, 1 and 2 hours after the first dose of propranolol, and 1 and 2 hours after each dosage increase of \(\geq 0.5\) mg/kg per day.
- Administration of propranolol with feedings, and holding doses if oral intake is compromised, reduces the likelihood of hypoglycemia.
- Topical application of timolol has shown efficacy in the management of superficial IHs.

Corticosteroid Therapy

The precise mechanism of action of glucocorticoids in the treatment of IHs remains largely unknown. Evidence suggests that corticosteroid therapy has several effects on IH, involving both vasculogenesis and adipogenesis. The diversity of these effects may account for the variability in response, particularly with the stage of the treated lesion. Steroids inhibit neovessel growth in cultured human IH biopsies197 and IL-6-mediated neovascularization in a rat corneal model.198 Corticosteroids also inhibit the expression of proangiogenic proteins, including VEGF-A, urokinase plasminogen activator receptor, monocyte chemoattractant protein-1, IL-6, and MMP-1, from human IH stem cells in a murine model.40,197 In addition, glucocorticoids inhibit the antiadipocytic differentiation effect of peroxisome proliferator activated receptor.201,202 This activity is thought to explain the development of the fibrofatty residuum during involution of the vascular components of IH.

Systemic Corticosteroids

Systemic therapy with corticosteroids for large and complicated IHs has, in many centers, been supplanted by systemic \(\beta\)-blockers. Nevertheless, steroids have played a significant role in IH management over the past few decades, and properly dosed and monitored, they remain an effective modality in the management of IH, especially in patients in whom \(\beta\)-blocker therapy is risky or contraindicated.203 One report in 60 children with IHs treated with either 3 or 5 mg/kg per day of oral prednisone found an excellent response in 68% and a good response in 25%; therapy failed in 7%.204 A systematic literature review showed an 84% response rate at an average dose of 2.9 mg/kg per day of oral prednisone.205 Another recent article reported the response to systemic corticosteroids was significant in 30% to 53% of cases, equivocal in 35% to 40%, and negligible in the remainder.206 In a prospective, randomized, investigator-blinded trial comparing prednisolone and propranolol dosed at 2.0 mg/kg per day, the drugs...
showed similar efficacy for reducing the area of symptomatic IH; however, although prednisolone showed a somewhat faster response rate, propranolol was better tolerated with significantly fewer severe adverse effects.207 Rebound growth occurs in 14% to 37% during dose tapering, occasionally requiring the resumption of steroid therapy.205 This wide range in rebound rates likely reflects the varied duration of corticosteroid therapy reported in the literature.

Optimal dosing of systemic corticosteroids remains somewhat controversial. However, although recommendations for prednisolone dosing have ranged from 2 to 5 mg/kg per day,132,203,204,208,209 optimal dosing appears to be 2 to 3 mg/kg per day. The duration of therapy depends on response rate as well as the age of the patient and phase of IH growth but generally ranges from 4 to 12 weeks at full dose, followed by tapering over several months and completion of treatment by 9 to 12 months of age.132,205

**Intralesional Corticosteroids**

The effectiveness of intralesional corticosteroid therapy for problematic IHs was first described in 1967 by Zarem and Edgerton,153 in the same article in which they reported their success treating IH with oral corticosteroids.

Subsequently, numerous studies have suggested that intralesional corticosteroid injection is a safe and effective treatment of IH.210–219 In general, corticosteroid injection is reserved for small, bulky, well-localized IH lesions. Large or diffuse IHs are more difficult to manage with intralesional corticosteroids because of the following: (1) a large volume of injectable steroid is more likely to cause systemic adverse effects220 and (2) it is difficult to evenly distribute the corticosteroid throughout a large tumor. In lesions that are relatively flat or superficial, intralesional steroid injection carries an increased risk of localized complications involving the overlying skin or underlying tissues. However, in appropriately selected lesions, many authors consider intralesional corticosteroid injection an effective intervention, given its effectiveness and the relatively low frequency of reported systemic adverse effects at low doses (≤2–3 mg/kg).210–219

In most studies, patients were injected with either triamcinolone alone or a mixture of triamcinolone and betamethasone, at total equivalent doses of triamcinolone doses of <3 mg/kg, by using a 27- or 30-gauge needle.218 The interval between injections varied from 1 to 6 weeks.208 After corticosteroid injection, large studies have reported accelerated regression in 77% to 100% of patients with IH and cessation of growth in 16% to 23%.210–219 The effects of the steroid last approximately 3 to 4 weeks216 and thus patients may require additional treatments during the proliferating phase for rebound growth.

Local complications of intralesional corticosteroids include fat and/or dermal atrophy and/or hypopigmentation (0%–3%).213–215 Systemic adverse effects, including cushingoid features (0%–3%)213–217 and adrenal suppression,220 can occur when very large doses of intralesional steroids are given (≥5 mg/kg). A more serious complication of intralesional corticosteroid therapy occurs in lesions of the upper eyelid, with 3 cases of retinal embolization having been reported after an injection of corticosteroids into IHs in this region.221–223 This complication likely results from a combination of high injection pressures (causing retrograde flow of the drug from the eyelid toward the apex of the orbit) and excessive injection volume.224 However, in several large series of intralesional corticosteroids for periocular lesions, this complication was not reported. Avoidance of this complication is discussed further in the subsection "Eye and Orbit" under "IHs With Special Anatomic Concerns."

**Topical Corticosteroids**

The use of high-potency topical corticosteroids in IH is usually limited to thin, superficial lesions. In the initial reports in the 1990s, topical clobetasol propionate was used for periocular IHs with good efficacy and no significant adverse effects.225,226 A subsequent retrospective chart review of 34 infants with proliferating IHs who had been treated with high-potency topical steroids found that 35% of the infants had good response, whereas 38% had a partial response.227 A more recent comparison of topical mometasone furoate versus intralesional triamcinolone acetonide in superficial IHs less than 5 cm in diameter showed that 86.5% (50% excellent, 36.5% good) of patients in the topical group and 95.7% (63.8% excellent, 31.9% good) in the intralesional group responded to the therapy.228

**TABLE 6 Potential Adverse Effects of Systemic Corticosteroids**

<table>
<thead>
<tr>
<th>Adverse Effect</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPA axis suppression</td>
<td>Weight gain/increased appetite</td>
</tr>
<tr>
<td>Cushingoid features</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Growth deceleration</td>
<td>Gastric irritation</td>
</tr>
<tr>
<td>Weight gain</td>
<td>Irritability</td>
</tr>
<tr>
<td>Increased appetite</td>
<td>Insomnia</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Immune suppression</td>
</tr>
<tr>
<td>Gastric irritation</td>
<td>Cardiomyopathy</td>
</tr>
<tr>
<td>Irritability</td>
<td>Steroid myopathy</td>
</tr>
<tr>
<td>Insomnia</td>
<td>Osteopenia</td>
</tr>
<tr>
<td>Immune suppression</td>
<td>Ocular adverse effects (glaucoma, cataracts)</td>
</tr>
<tr>
<td>Cardiomyopathy</td>
<td>Cushingoid features (0%–3%)</td>
</tr>
<tr>
<td>Steroid myopathy</td>
<td>Adrenal suppression</td>
</tr>
<tr>
<td>Osteopenia</td>
<td>HPA, hypothalamic-pituitary-adrenal</td>
</tr>
</tbody>
</table>

**Adverse Effects of Corticosteroid Therapy**

Potential systemic adverse effects of corticosteroids used in the treatment of IH are presented in Table 6 and are the most common reason cited for using propranolol as first-line therapy. It should be noted, however, that a few physicians have favored the safety profile of corticosteroids over that of propranolol.229
Suppression of the hypothalamic-pituitary-adrenal axis has been observed during therapy with both intraleasional\(^{215-217,220,230,231}\) and systemic\(^ {132,232-236}\) steroids. However, incidence estimates for hypothalamic-pituitary-adrenal axis suppression vary widely, from 1.7\(^ {222}\) to 87\(^ {234}\). Furthermore, although many patients experience abnormal morning cortisol levels, nearly all appear to normalize in a few months.\(^ {220,231}\)

Temporary growth deceleration has also been reported with both intraleasional\(^ {218,220,232}\) and systemic\(^ {132,236,237}\) steroid therapy of IHs. Almost all children experience “catch up” growth after completion of therapy.\(^ {236}\) Gastric irritation is seen in 21\(^ {236}\) to 32\(^ {234}\) of patients taking oral corticosteroids. This adverse effect can be ameliorated by concomitant use of H\(_2\)-receptor antagonists.\(^ {132,215,218}\) Mild behavioral changes have been seen in up to 29\(^ {9}\) of infants receiving systemic corticosteroid for IH therapy.\(^ {236}\) These include irritability, fussiness, insomnia, and personality changes.\(^ {230,234,236,237}\)

Osteopenia is a known adverse effect of long-term systemic corticosteroid therapy but is rarely observed in children with IH, which presumably is related to the relatively short duration and nonrepetitive nature of therapy typically used for the treatment of IHs. Hypertension is also a risk of systemic corticosteroid therapy, but the percentage of affected individuals is unknown and is likely dose dependent.

Immunosuppressive effects of systemic corticosteroid therapy are well known. These include increased infection risk, reduced B- and T-lymphocyte counts, and poor response to vaccines.\(^ {132,218,236,237}\) Rare cases of pneumonia attributable to *Pneumocystis carinii* infection have been reported in infants taking corticosteroids for IH, and prophylaxis of these patients with trimethoprim-sulfamethoxazole has been advocated by some experts.\(^ {238-240}\)

Furthermore, it has been suggested that infants not receive live vaccines during long-term corticosteroid therapy and that clinicians consider checking vaccine titers on completion of corticosteroid therapy to assess the adequacy of response.\(^ {237}\)

Ocular adverse effects of long-term systemic corticosteroid therapy include cataracts\(^ {241,242}\) and increased intraocular pressure,\(^ {242-245}\) although neither has been frequently reported among children in general or among those being treated for IH in particular. The most serious ocular adverse effect is that of vision loss caused by embolic occlusion of the central retinal artery after intralesional injection.\(^ {221-223}\) However, the actual risk is thought to be quite low and is primarily related to high injection pressure.\(^ {224,246,247}\)

This complication is discussed in greater detail in the subsection “Eye and Orbit” under “IHs With Special Anatomic Concerns.”

Cutaneous adverse effects of steroids are most often associated with intralesional and topical therapy. The most common risks are atrophy and hypopigmentation, although the former is often attributable to the IH itself, whereas the latter is usually transient.\(^ {227,233}\) Other potential but unusual risks include acne, periorificial dermatitis, striae distensae, and hypertrichosis. In treating bulky IHs with intralesional therapy, cutaneous complications can be avoided by keeping the injection well below the dermis.

Given the many potential adverse effects of glucocorticoid therapy, many physicians will periodically reevaluate those infants receiving systemic corticosteroids (oral or intralesional), with specific attention to growth variables and blood pressure. Some physicians will also reassess adrenal function at the end of therapy and determine the need for stress doses of steroids on cessation of therapy.

### Highlights of This Section

- Despite their efficacy, systemic corticosteroids are no longer considered by most clinicians to be first-line therapy for IH due to the associated risk of adverse effects.
- Corticosteroids, administered orally at a dose of 2 to 3 mg/kg per day, are efficacious in reducing size and discoloration of IH.
- The mechanism of IH growth inhibition by corticosteroids likely involves reduced vasculogenesis and enhanced adipogenesis.
- Corticosteroids administered intralesionally and topically also appear to be effective in certain subsets of patients with more localized IH, but their dosing and safety profile are not well studied.
- Periodic reexamination of children receiving corticosteroid therapy for IH has been suggested for monitoring of growth and blood pressure as well as changes in the lesion(s) being treated.

### Other Medical Therapies

Before the discovery of the therapeutic efficacy of propranolol for IH, several other agents were used in an attempt to optimize efficacy and safety. This section will focus on 3 agents that have documented utility in the treatment of IH: vincristine, interferon-\(\alpha\), and imiquimod. Unfortunately, the adverse effect profiles of these agents limit their usefulness, and they are generally reserved as treatments only for recalcitrant lesions. In addition, the potential usefulness of newer angiogenesis inhibitors will be discussed.
Vincristine

Vincristine is a plant-derived vinca alkaloid that impairs mitosis via microtubule formation. It has traditionally been used as a chemotherapeutic agent and possesses multiple antiangiogenic qualities. It induces endothelial cell apoptosis and is also a potent inhibitor of endothelial cell growth, migration, and in vitro capillary-like tube formation. Given that endothelial cells also possess a high tubulin content, a biological rationale for IH sensitivity to vincristine exists. Most reports on the efficacy of vincristine address the treatment of patients with vascular lesions that were not true IHs but rather KHE or TAs associated with KMP. However, vincristine has also been used successfully in the management of function-threatening or life-threatening IHs (airway, orbital, or hepatic). The drug is administered weekly through a central catheter because of its extreme vesicant and irritative potential. Adverse effects include alopecia, rash, and myelosuppression are also possible. Reported adverse effects were transient. This drug appears to be particularly useful in patients with corticosteroid-resistant KMP, but it is not a first-line therapy for IH.

Interferon-α

Interferon-α 2a and 2b have both been used successfully for IH in children. Interferon-α is given subcutaneously with an initial dose of 1 million IU/m2, increasing to 3 million U daily over the first month of therapy while monitoring neurologic status, white blood cell count, and liver function status. Most patients have required between 2 and 12 months of therapy. Adverse effects are significant and include flulike reactions, rash, gastrointestinal symptoms, transaminitis, neutropenia, and spastic diplegia. Although some have reported response rates of up to 90% in steroid-resistant lesions, the effect is gradual in onset, and rebound can occur on discontinuation.

Up to 20% of children treated with interferon-α appear to develop spastic diplegia. This complication tends to occur later in the treatment course and may be irreversible. Some practitioners initially theorized that only interferon-α 2a, or perhaps the preservative or vehicle, were the cause of these symptoms; however, similar toxicities have also been reported with interferon-α 2b. Given these concerns, interferon-α is generally considered a “last resort” treatment, and most physicians prefer to use propranolol, systemic corticosteroids, or vincristine before treating with this agent.

Imiquimod (Imidazoquinoline 5%)

This topical immune-response modifier stimulates the innate immune system by augmenting the production of cytokines, including interferons (α, β, and γ); IL-10, IL-12, and IL-18; and tumor necrosis factor. These agents enhance cell-mediated immunity and induce apoptosis. However, it may well be that imiquimod’s therapeutic effect on IH results from the inhibition of angiogenesis by these cytokines. In addition, imiquimod downregulated proangiogenic factors such as bFGF and MMP-9 and upregulated other endogenous angiogenesis inhibitors, including interferon-inducible protein 10, tissue inhibitor of MMPs, and thrombospondins. Topical application of imiquimod has been shown to markedly inhibit tumor cell–induced angiogenesis in a human keratinocyte model. In 2002, the successful use of imiquimod was reported in the treatment of scalp IHs. Subsequently, a retrospective study reported the efficacy of topical imiquimod in 18 children with IH.

The drug was used 3 times weekly in 10 patients and 5 times weekly in 8 patients, with a mean duration of therapy of 17 weeks. All superficial IHs improved, but little or no change occurred in mixed and deep IHs. Irritation and crusting were the most common adverse effects. This study was criticized because of the lack of a control group. A subsequent phase II, open-label study followed 16 children with mixed results. Although some proponents of imiquimod continue to use it for the treatment of superficial IH, irritation, crusting, and occasionally significant ulceration noted with treatment seriously limit its utility. Imiquimod does not have a role in the treatment of deep IHs.

Antiangiogenic Agents

Although all of the above treatments have antiangiogenic effects, a few newer therapies have specific antiangiogenic mechanisms of action that make them theoretically attractive therapeutic options. Antagonists to vascular growth factors or receptors, such as inhibitors of VEGF or bFGF, have been successfully used to blunt angiogenesis in tumor models and as therapies for advanced neoplasms; however, the simultaneous administration of cytotoxic agents appears to require to achieve significant response rates. An incidental decrease in the size of a liver IH was noted in a patient treated with bevacizumab, a VEGF inhibitor. Most recently, the antivasculogenic effect of rapamycin has been shown in a mouse hemangioma model; the drug diminished the self-renewal capacity of the IH stem cells while simultaneously inducing other antiangiogenic effects on IH endothelial cells. Rapamycin is a macrolide known to have both immunosuppressant and antiangiogenic actions, and therefore the risk-benefit ratio of this agent will need to be clearly established before it.
can be considered a safe alternative to the agents currently available for the treatment of IH.

**Highlights of This Section**

- Medications other than β-blockers and corticosteroids may have efficacy in treating IH, but their utility is limited by their safety profile.
- Vincristine is used for lesions associated with KMP; however, such lesions are KHEs and TAs rather than IHs and are associated with potential risks of irritation and neurotoxicity.
- Interferon-α and imiquimod, although effective in IH treatment, are associated with an undesirable rate of complications.

**LASER THERAPY FOR IH**

Before the discovery of the efficacy of propranolol in the treatment of IH, PDL therapy was frequently a component of the treatment strategy for IHs. However, given their limited depth of penetration of less than 2 mm, these lasers proved useful primarily for superficial lesions and for deep and compound lesions in which salvage of the superficial skin was desired. Although many such lesions are now treated medically, laser therapy may still have a role in IH management, particularly when used as a part of multimodal therapy or in ulcerating lesions refractory to other therapies. In the 1980s, technological advances imparted to lasers the capability of selective photothermolysis, a process by which blood vessels are selectively destroyed while causing minimal collateral damage to surrounding tissue. For laser light to be optimized for this purpose, it needed to be of an appropriate wavelength for absorption by hemoglobin and of an appropriate exposure time to avoid the generation of excess thermal energy in adjacent tissues. As indicated in these reports, PDL achieves these parameters and has become the “workhorse” laser in the treatment of superficial vascular lesions.

PDL was developed primarily for the treatment of port wine stains. IHs differ greatly in many respects. Although port wine stains are malformations made up of low-flow, thin-walled ectatic postcapillary venules, IHs are tumors made up of small capillaries lined with plump endothelial cells and have a higher rate of blood flow. IHs are also of more varied thickness. As a result, improvement in IH with the use of PDL is somewhat less predictable than that for port wine stains. The mechanism for laser destruction of IHs has not been completely elucidated.

PDL has undergone multiple improvements since it was first introduced. Current models use a wavelength of 595 nm and larger spot sizes (up to 10 mm) with higher fluences, allowing the laser to penetrate deeper. Longer pulse durations facilitate the treatment of larger vessels. In addition, the introduction of dynamic cooling delivered to the skin before the laser pulse has made treatment safer and less painful.

In the 1990s, many laser proponents embraced the theory that early laser treatment could eradicate superficial proliferating lesions and, at the very least, reduce the discoloration of the superficial component of a mixed IH. As a result, children often received multiple laser treatments during their first year of life. However, a 2002 study in 120 children randomly assigned to laser treatment or observation found that the complete clearance or presence of minimum residual IH at 1 year was not significantly different in the PDL-treated and observation groups.

Although these findings have been disputed, another article authored by leading laser authorities suggested that infants were particularly susceptible to complications from PDL treatment. The controversy over laser use was recently rekindled by a study that showed an advantage to early laser management.

Although small IHs may be treated without sedation, children with larger lesions often require general anesthesia. Recent data suggest that early exposure to general anesthesia may have a negative effect on learning and behavior. As a result, repeated anesthetics required to treat such lesions may be less desirable when the likelihood of improvement is low and other available treatment options are available.

Proposed uses for PDL in IH management include the following: (1) early superficial facial IHs, (2) treatment of compound IHs in which sacrifice of the overlying skin is undesirable, (3) refractory ulceration, and (4) significant residual telangiectasia or flat IH persisting after involution.

**Early Superficial IHs**

Although not all superficial lesions warrant intervention, early treatment in cosmetically critical areas can reduce or eradicate a superficial dermal IH, allowing the return of normal dermis and preventing the atrophic scarring commonly observed after involution. Although topical β-blocker therapy is also an option in managing small superficial IHs, there may be greater bioavailability of the drug when treating infants, particularly those with IHs that have ulcerated or are located near mucous membranes.

PDL is a treatment option in such cases.

**Treatment of Critical Skin**

In certain anatomic locations, the sacrifice of skin that is atrophic or...
still contains IH tissue is undesirable. The face, and the nasal tip in particular, are areas in which the removal of affected skin may leave undesirable scars or a poor color match with grafted skin. In such cases, early laser treatment may preserve the overlying skin, allowing it to be later lifted as a flap to provide access for excision of the deeper IH (demonstrated in Fig 17 later in report).

**Treatment of Ulcerated IH**

The potential benefit of, and evidence for, laser treatment of ulcerated IH has previously been discussed (see the previous section entitled “Management of Ulcerated IHs”). In most cases, such intervention is a consideration only after medical management has failed.

**Persisting Telangiectasia or IH After Involution**

After treatment or involution of IH, superficial vascular ectasias frequently remain. These are effectively treated with PDL. PDL may also be used to treat flat areas of residual IH tissue.

**Complications of Laser Therapy**

Complications of laser treatment include atrophic scarring and hypopigmentation, particularly in individuals of darker complexion. Lasers are also capable of inducing ulceration, although this is rare and seen more commonly in rapidly proliferating IHs and segmental IHs, which, if left untreated, also have a higher risk of ulcerating spontaneously. Scarring is seen when the dermis between the vessels is coagulated. An IH in which the dermis is largely replaced by vessels, efficient photococagulation of these vessels will lead to scarring. Although the complication rate of PDL use for IH has not been studied, it is less than 1% in the treatment of port wine stains.

**Highlights of This Section**

- Laser treatment of IHs may be useful in early, non-proliferating, superficial lesions; management of critical skin; treatment of ulcerating lesions; “multimodal” therapy; and management of persisting postinvolution telangiectasia.
- Pulsed dye laser (PDL) is used most commonly because its light is preferentially absorbed by hemoglobin.
- Use of laser on proliferating and superficial IHs may lead to ulceration.
- Atrophic scarring and hypopigmentation are also potential complications of laser use in IH.

**SURGICAL THERAPY FOR IH**

**Timing of Intervention**

Eelective resection of an IH during the proliferative phase is usually not necessary and occasionally ill advised. Given their young age and the vascularity of the tumor, affected patients are at greater risk of anesthetic morbidity, blood loss, and iatrogenic injury. In addition, in many 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. However, certain factors lower the threshold for resection of a cosmetically or functionally problematic lesion during early infancy, including the following: (1) contraindication to pharmacotherapy, (2) failure of pharmacotherapy to ameliorate the problem, (3) focal involvement in an anatomically favorable area, and (4) a high likelihood that resection will be necessary in the future (due to bulk or ulceration) and the scar will be the same.

During the involution phase of IH, children are reevaluated periodically if it is likely they might require excision of residual fibrofatty tissue, resection of scarred/excess skin, or reconstruction of damaged structures. A residual scar will always be present after ulceration of an IH and may therefore lower the threshold for surgery in some cases. Similarly, those lesions likely to leave large fibrofatty residua may be addressed early. Surgery is rarely an option for extensive IHs from which the resulting defect is too large to close primarily or for those cases in which surgery will result in significant functional impairment or an unacceptable scar. Conversely, resection of small, complicated IHs in cosmetically favorable locations may occasionally be preferable to months of observation and/or medical therapy. As discussed earlier, the timing of intervention is based on the age of the patient, the degree of deformity, and whether the tumor is still regressing. If a child has a minor deformity, postponing intervention until maximal involution has occurred may obviate the need for a procedure. Following the patient for as long as possible may also be indicated for lesions in problematic locations (eg, lip or nasal tip), because maximal involution may facilitate reconstruction and reduce the number of required interventions.

Once it is obvious that a child will require operative intervention, surgery is usually preferable in early childhood (≤4 years of age), before the child has much awareness of the lesion. However, by postponing intervention until at least 3 years of age, the tumor has had time to involute, often facilitating the procedure and improving the final cosmetic result.

**Location Considerations**

For an IH that causes a deformity that cannot be easily concealed (eg, on the face), surgical intervention may be
considered in early childhood to prevent psychosocial morbidity. If the tumor is hidden by clothing and is not bothersome to the child, waiting for maximal involution to occur is acceptable. When considering resection, it is important to weigh the postoperative scar after removal of the IH against the preoperative appearance of the lesion. Linear scars are ideally placed along the relaxed skin tension lines in the anatomic area where the IH is located to facilitate the best possible cosmetic outcome.

Certain anatomic locations present specific challenges to the surgeon. IHs of the auricular helix and nasal tip involve skin that does not move well over the underlying cartilage and is difficult to replace. Lesions of the lip that extend outside the vermilion may require reestablishment of the vermilion-cutaneous border as well as the natural labial contours. Surgery involving the eyelids, oral commissure, and genitalia also carries a risk of functional impairment from the procedure itself.

**Technical Considerations**

Because an IH itself acts as a tissue expander, there is usually adequate skin to allow primary, linear closure of the wound; skin grafts and local flaps are rarely needed. Because the tumor is benign, the entire lesion does not need to be removed; the goal is to improve the appearance of the child and subtotal excision is often performed. For circular lesions located in visible areas, the length of the scar and distortion of surrounding structures can be minimized by circular excision and purse-string closure.²⁹³ Although lenticular excision of such a lesion will result in a scar 2 to 3 times the diameter of the original IH.²⁹³ This technique can also be used to alter a vertical forehead scar to a horizontal orientation. In the scalp, lenticular excision and linear closure is preferred to circular excision/purse-string closure because a long linear scar is camouflaged by hair; whereas a circular scar may leave an area of visible alopecia.²⁸⁸ Fibrofatty residuum from the deep component of an IH can be removed by using suction-assisted lipectomy; similar lesions on the cheek can occasionally be approached intraorally to avoid a major cutaneous scar.

**Highlights of This Section**

- Indications for surgery for IH during infancy are limited to the following:
  1. failure of, or contraindication to, pharmacotherapy;
  2. focal involvement in an area anatomically favorable for resection; and
  3. a high likelihood that resection will ultimately be necessary and the scar will be the same regardless of timing.

- During involution, surgery may be indicated for excision of residual fibrofatty tissue, resection of scarred/excess skin, and/or reconstruction of damaged structures.

- Timing of surgery is based on the age of the patient, the location and degree of deformity, and whether the tumor is still regressing.

- Elective surgical intervention for IH is reasonable after age 4 years because, by this age, self-esteem and long-term memory begin to form and the tumor has completed most of its involution.

**IHS with Special Anatomic Concerns**

**Eye and Orbit**

IHs of the orbit, eyelid, and conjunctiva, also known as periocular IHs, have the potential to cause a unique set of vision-related complications because of their anatomic location. Compression of the globe, obstruction of the visual axis, and extension into the retrobulbar space have the potential to cause refractive errors, strabismus, and amblyopia. Although evaluation and management follow principles common to all IHs, additional considerations in these cases strongly influence clinical decision-making.

The importance of early ophthalmologic assessment of patients with periocular IH cannot be overemphasized. Ophthalmologic consultation is often necessary to determine the urgency of intervention. In addition, the full depth of these lesions within the orbit is often underappreciated on routine physical examination, as are visual field cuts and changes in refraction or extraocular motion.

Amblyopia is the most common and most serious ophthalmic complication of periocular IHs. This disorder results when, because of improper stimulation of the involved eye, the portion of the brain serving that eye does not develop properly. Amblyopia occurs in 43% to 60% of
children with untreated periocular IHs, usually as a result of visual deprivation or refractive errors.294–296

Deprivation amblyopia occurs when a bulky IH, usually in the upper eyelid, completely obstructs visual input into the involved eye. The lack of input causes a maldevelopment of visual pathways and may result in irreversible loss of vision.297

Refractive errors are due to astigmatism or anisometropia. Astigmatism is the production of a blurred image on the retina due to altered curvature of the cornea and occurs in 20% to 46% of patients with periocular IHs.298 IHs causing this disorder usually involve the upper lid294 (Fig 14) but may occur in the lower lid as well. The astigmatism can be reversed with early intervention, preferably before 9 months of age. Beyond 13 months of age, astigmatism typically persists despite involution of the IH;295,296 however, some cases of improvement during involution have also been reported.299–301 Anisometropia is a difference in refractive error between the eyes that results in a relatively clear retinal image in the eye with the smaller refractive error and a relatively blurred retinal image in the eye with the larger refractive error. Although children with refractive errors attributable to IH can be treated with contralateral patching regimens, many still develop permanent spectacle dependence; in many cases, the brain may ignore the blurry image in the involved eye, resulting in amblyopia.

Strabismus, or misalignment of the eyes, occurs in approximately one-third of children with untreated periocular IHs.294 Strabismus may result from deprivation amblyopia, mechanical obstruction of extraocular muscle movements, or direct extraocular muscle invasion. Medial rectus involvement is most common and most obvious, producing esotropia. Superior oblique involvement is common in typical supronasal eyelid and orbit cases, but the strabismus is subtle and requires forced ductions or other testing to diagnose.

Permanent eyelid deformity results from direct invasion, vascular steal, or prolonged pressure of adjacent structures, including the levator palpebrae superioris, tarsus, eyelash follicles, and lamina papyracea. The levator muscle can be salvaged with early treatment, but prolonged invasion produces a fatty, atrophic muscle akin to true congenital ptosis. Tarsus, lash follicles, and the bones of the orbit also respond well to early intervention because the ongoing anatomic destruction or deformity can be arrested at a very early stage. Preservation of the tarsus ensures eyelid margin stability, whereas maintenance of the bony socket prevents enophthalmos and facial asymmetry.

Proptosis is the forward displacement of the globe from an intraorbital IH. Occurring in approximately one-third of children with orbital IHs, proptosis can result in impaired approximation of the eyelids and corneal exposure. Optic neuropathy may also result from compression or stretching of the optic nerve.294

Patients with PHACE syndrome may present with a unique set of ophthalmologic abnormalities, including increased retinal vascularity, microphthalmia, optic nerve hypoplasia, exophthalmos, chorioid hemangiomas, strabismus, colobomas, cataracts, and glaucoma. Twenty percent of affected patients will have at least 1 of these findings, often on the side contralateral to the IH.118

Alternatives available to treat periocular IHs mirror general treatment options, but special regional factors may influence the final treatment plan. Urgency, laser safety, and the luxuriant vascularity of the region all influence the treatment method selected.

As with most IHs, treatment with propranolol has become the mainstay of systemic therapy for periocular lesions. Numerous case series suggest success not only in controlling the growth and size of the lesion but also in improvement of astigmatism.302–304 Unfortunately, perceived successes with propranolol therapy may, in some cases, lead to delayed ophthalmologic referral for more subtle sequelae, resulting in irreversible changes and limiting treatment alternatives, underscoring the need for early ophthalmologic evaluation.

Before the advent of propranolol, intralesional steroid injection was a popular intervention for the management of bulky periocular IHs.299 With the use of a combination of triamcinolone and betamethasone, a response within 2 weeks could be anticipated in 60% to 80% of patients.305 However, intralesional steroids have been associated with a number of complications. Most feared is embolism of the central retinal artery.221–223 This complication is thought to result from several factors, including high injection pressures (causing retrograde flow of the drug from the eyelid toward the apex of the orbit), excessive injection volumes, and direct intravascular injection.224,246,247 Although it has been argued that high pressures can be avoided by using a large-capacity syringe and small bore cannula,306 studies suggest that even these precautions may be insufficient in preventing embolization.224 Other reported complications include hypopigmentation, atrophy of subcutaneous fat, and full-thickness eyelid necrosis.307–310 With improvements in systemic medications and surgical techniques, many now believe that there are better options for the management of periocular IHs.
Topical use of timolol has shown efficacy in the management of superficial periocular IHs, as well as IHs involving the conjunctiva and iris. This drug has replaced other topical therapies such as imiquimod, which causes significant irritation of the skin, conjunctiva, and cornea, and topical steroids, which carry the risk of glaucoma and cataract formation. Laser treatment (PDL) can also be very effective in treating superficial periocular IHs but usually requires corneal protection and general anesthesia.

Periocular IHs are often diffuse and are therefore difficult to excise. Surgery can also cause hemorrhage that complicates the surgery and can cause postsurgical changes, such as ptosis and entropion, which may be difficult to correct. However, early surgical removal, in selected lesions, eliminates the risk of amblyopia, decreases amblyopia treatment times, and dramatically improves the chances for extraocular muscle, eyelid, and orbit preservation. For periocular IHs that are considered for surgical resection, preoperative imaging aids in establishing the extent of the lesion. Those that are best suited for surgery are located outside the bony orbit and well circumscribed and noninfiltrative on MRI.

Airway

IHs can involve any part of the airway. The exact incidence of airway IH is unknown; however, over a 4-year period, 33 freestanding US children’s hospitals discharged an average of 2.5 patients with this diagnosis who had undergone an airway procedure. Symptomatically, airway IH usually manifest during the period of rapid growth during the first few months of life. A total of 80% to 90% of affected infants will present within the first 6 months of life, with a mean age of 3.6 months at diagnosis. Most develop biphasic stridor and barking cough as the IH enlarges in the subglottis, the narrowest portion of the pediatric airway (Fig 15). Voice and swallowing are generally normal. Often, the symptoms are mistaken for those of infectious or inflammatory croup or reactive airway disease, especially when the symptoms worsen in the presence of upper respiratory illness. As a result, symptoms are often present for several weeks before a definitive diagnosis is made.

Approximately half of infants in whom an airway IH is diagnosed also will have a cutaneous IH, but only 1% to 2% of children with cutaneous IHs also have airway IHs. Symptomatic airway IHs can be associated with lower facial cutaneous or oral/pharyngeal mucosal IHs in approximately 50% of cases.

Most infants suspected of having an airway IH on the basis of historical and clinical presentation undergo operative endoscopy. Imaging of the head and neck may be useful in some cases to confirm the diagnosis of IH, to define the extent of the airway lesion, or to detect any associated vascular, brain, or chest anomalies that could affect treatment. Because these airway lesions have a characteristic clinical and endoscopic

**FIGURE 15**
Airway IH extending from the vocal folds inferiorly into the subglottic space, the narrowest region of the pediatric airway. (Photo courtesy of Jonathan Perkins, DO.)
appearance, biopsy of airway IH is not usually necessary, but when performed, the histologic appearance and cellular markers are the same as those of cutaneous IH.323,324 As in cutaneous IH, airway IH can be localized (focal) or extensive (segmental), and many subglottic lesions show transglottic or paratracheal extension.308,314 The more extensive the lesion, the more significant the airway compromise, and aggressive therapy is usually necessary to prevent airway obstruction.

The need for and type of intervention for airway IH is determined by several factors, including the degree of airway obstruction, the extent of extralaryngeal IH, the location of the patient at the time of diagnosis, the experience of the treating physician, and the preferences of the parents/caregivers. Because involution is the ultimate fate of virtually all IHs, “watchful waiting” is reasonable in cases involving minimal symptomatology. In rare symptomatic cases for which observation is still preferred or pediatric airway expertise is not readily available, tracheotomy is occasionally necessary.325 However, in most cases, some alternative intervention for the IH is more desirable.

Before the advent of propranolol therapy, endoscopic laser ablation or surgical excision was often recommended in the management of airway IH, because the only medical therapy was long-term corticosteroids.317,326–330 However, many clinicians have now reported success and low complication rates using propranolol in the management of airway IHs.326,331–336 Although the optimal dose and appropriate duration of therapy remain uncertain, most clinicians are dosing the drug as they would for cutaneous IH.337 Some authors have suggested that treatment with propranolol should become the standard for initial management of all airway IHs.338

Corticosteroids may be helpful in refractory cases. Initial doses of prednisolone at 2 to 4 mg/kg per day are generally necessary to control growth. Maintenance doses of approximately 1 to 2 mg/kg per day are often considered before weaning the medication, and treatment duration is based on clinical response. Response rates reported in the literature vary between 30% and 93%, although there is little consistency among dosing regimens.339

Intralesional steroids are a consideration for patients whose IHs have necessitated endoscopy or endoscopic resection. Although repeated injections are usually necessary as single-modality therapy,327 these medications may be effective adjuvant therapy for patients whose lesions are being observed, treated pharmacologically, or partially resected. Successful management has been achieved in 77% to 87% of cases with the use of intralesional steroids.317,327

Airway IHs causing focal obstruction may be addressed surgically by a subtotal endoscopic approach by using a microscope or telescope or by total excision through an open approach. Subtotal approaches generally use a laser341 or rotary-powered instrument.340 However, subtotal resection carries the risk of growth of the residual lesion during the proliferative phase, and laser treatment carries a 5% to 25% risk of subglottic stenosis that is greatest with deeper resections and in cases of bilateral or circumferential disease.326,341,342

Open surgical excision of a focally obstructing airway IH became popular in the 1990s, after complications of laser therapy became increasingly apparent.329,343–345 The procedure is useful in cases refractory to medical therapy and may be preferable to laser in patients with bilateral or circumferential lesions who may be at risk of postoperative stenosis or require tracheotomy. However, open surgical excision may be more difficult in cases involving significant extension outside the larynx, and the procedure may potentially result in some degree of dysphonia.

**Highlights of This Section**

- Most patients with IHs of the airway have subglottic involvement causing biphasic stridor and barky cough, often mistaken as croup. Voice and swallowing are generally normal.
- Diagnosis of airway IHs is usually made by endoscopy in the operating room.
- In most cases, IHs of the airway may be managed medically; in cases of severe obstruction, surgical resection may be entertained.

**Nose**

Nasal IHs deserve special attention for several reasons. First, the prominence and central location of the nose make it a critical facial feature. As a result, even a small IH of the nose can have a greater effect on appearance than a lesion of the same size located elsewhere. In addition, damaged nasal tip skin is exceedingly difficult to excise or replace without considerable cosmetic consequence. Functionally, a nasal IH may also cause collapse of the nasal introitus and intranasal obstruction.

Focal nasal IHs account for 15% to 20% of all focal IHs of the face; of these, approximately one-third involve the nasal tip.91 These lesions appear to have their origin in the intercartilaginous ligament of the lower lateral nasal cartilages.346 As the IH grows, it displaces the
cartilages outward, rotating them in an "open book" fashion (Fig 16). The net effect is a bulbous, distorted nasal tip, which, even with complete involution of the IH, will remain disfigured. The deformity has been referred to as the "Cyrano" nose, after Cyrano de Bergerac, the French playwright known as much for his prodigious proboscis as for his dramatic works. Segmental IHs involving the nose typically affect more nasal subunits than their focal counterparts, and they are more likely to ulcerate, resulting in destruction of critical areas such as the columella and ala.

Conservative management of nasal IHs is associated with a poor outcome in most cases. As a result, early management of nasal IHs has been advocated to avoid complications and improve the likelihood of a favorable outcome, although the assumed benefit is yet unproven. The approach to nasal IHs is often multimodal, varying with the location, the stage, and the depth of the IH.

Medical therapy may commence once the diagnosis has been made and it is clear that the IH is growing. The duration of treatment will depend on the type of lesion and its response. Focal IHs that respond to propranolol are generally treated until at least 9 to 10 months of age, at which time growth of these lesions is likely to cease. Rebound growth may be addressed by restarting the medication for a month at a time until there is no further growth. Because segmental IHs may proliferate for longer periods of time, weaning is often delayed until 18 months of age; rebound may be addressed with additional treatment in 3-month intervals.

Propranolol-treated IHs of the nasal tip are less likely than untreated lesions to undergo surgery or laser therapy, but many lesions still require such interventions. Extensive skin involvement in focal lesions may respond to topical β-blockers or judicious use of laser (PDL) during proliferation (Fig 17). This treatment will salvage the skin by reducing the number of intracutaneous vessels and will also diminish the risk of venous stasis in

FIGURE 16
Open rhinoplasty approach to nasal tip IH. These lesions (H) originate within intercartilaginous ligament of the lower lateral nasal cartilages (arrows), rotating them outward.

FIGURE 17
A, Compound IH of the nasal tip with significant surface involvement. B, Nasal tip after treatment with PDL to salvage tip skin before surgical resection.
the deep component after surgical resection. It also helps to maintain more normal collagen and skin after proliferation has ceased. Similarly, for nasal lesions within segmental IHs that have failed to respond to medical therapy, it may be best to delay surgery until the overlying skin has been adequately treated. It is generally preferable to delay surgical intervention for such lesions until there is no further proliferation. PDL may also be used to treat residual involvement of the overlying skin after surgery.

Nasal IHs that fail to respond to propranolol or leave significant residual tissue after treatment are usually addressed surgically. Although some authors have advocated surgery for focal IHs as early as 10 to 12 months of age, most physicians will operate at 1 to 3 years of age. This approach allows for complete cessation of growth and adequate time for involution of small lesions that may ultimately cause no significant distortion of the tip.

Several publications have dealt with the surgical approach to nasal IHs. All of these publications predate the treatment of IH with propranolol, which has clearly changed the management paradigm. The major issues in surgery for IHs of the nasal tip relate to adequate access and the ability to dispose of the excess skin once the lesion has been removed. In general, smaller lesions may be addressed in a single procedure through an external rhinoplasty approach, leaving a scar only on the columella of the nose. Larger IHs may require external incisions on the ala, also described as a “modified subunit approach,” which simplifies excision and redraping of the skin. Surgery is also useful in restoring the normal position of the lower lateral cartilages and other components of the cartilaginous framework.

FIGURE 18
Ulc erated IH of the lower lip has resulted in distortion of the soft tissue and obliteration of the vermilion-cutaneous border.

Lips

The lips deserve special consideration in the management of IH due to their critical role in cosmesis and function. Distortion of the lips from IH is common, and restoring normal lip contour is one of the greatest challenges in reconstructive surgery. Furthermore, the lips (and the lower lip, in particular) are at increased risk of ulceration, resulting in pain and bleeding in the short term and in increased scarring and disfigurement in the long term.

During proliferation, the goals of managing IH of the lips are to minimize distortion and to control ulceration (Fig 18). Once ulceration occurs, some infants will have difficulty latching on to a breast or bottle nipple without discomfort, occasionally leading to failure to thrive. Furthermore, the vermilion of the lip is a unique tissue that cannot be replaced if permanently damaged by ulceration, and reconstruction of the normal lip contours after ulceration can be challenging. Proactive management of IH of the lip, often systemic, is vital if ulceration is to be avoided. However, in the lower lip, some 30% of IH lesions ultimately ulcerate. Once ulceration has occurred, occlusive dressings are impractical, and therapies such as topical anesthetics and petroleum-based products carry the risk of accidental oral ingestion. Occasionally, children with IHs on the lip benefit from laser treatment of the ulcer, but worsening of the ulceration is a risk. Early surgical resection is a consideration, but only for small ulcers in cosmetically favorable areas. Otherwise, attention is best directed to systemic therapies to reduce the likelihood of further ulceration and of excessive lengthening of the lip.

Reconstruction of a lip that is scarred and disfigured because of IH is best performed only after growth of the IH has definitively ceased, because...
recurrence is certain to interfere with recontouring. Furthermore, the mucosa of the mandibular oral vestibule is most useful for reconstruction of the vermilion when it is free of the IH.

Lesions located exclusively on the vermilion can be removed by using a transverse mucosal incision to hide the scar at the junction of the vermilion and vestibular mucosa; lesions traversing both tissues may require a vertical incision. Bulky lesions that cause lengthening of the lip and those that cross the vermilion-cutaneous border are best addressed by using a wedge excision, with some authors advocating a 2-stage procedure to improve scar camouflage. In such cases, incisions may be placed along the mucocutaneous junction or philtral columns. Debulking lip IH while preserving vermilion can be performed through a mucosal incision; however, it is often exceedingly difficult to separate IH from orbicularis oris muscle. Eversion of the lower lip can be corrected by excision of a mucosal strip, and correction of inversion may require a lyophilized dermal implant or dermal graft. Setting the “white roll” (ridge at the vermilion-cutaneous border) of the lower lip and restoring normal sublabial concavity may be particularly challenging.

Perineum

Although perineal area IHs occur in a nonconspicuous area, they are highly prone to ulceration. In case series from tertiary care dermatology practices, perineal IHs account for approximately one-third of all ulcerating lesions, and approximately 50% of IHs occurring in this area ultimately ulcerate. Perineal ulceration can, at least transiently, result in significant pain during defecation and urination and during diaper changes. Because surgical intervention involving structures in this area may be fraught with complications, management strategies generally focus on those topical and systemic medical remedies previously discussed (see “Management of Acute IH Ulceration”). In rare cases, colostomy has been performed to facilitate wound care.

Liver

The liver is the most common location for visceral IH. Research from the past decade has contributed greatly to the classification of hepatic tumors and to clarify their natural history. Previously viewed homogenously, and often treated inappropriately, it is now becoming clear which patients are at risk and what treatment options are sensible.

Patients at risk of hepatic and other extracutaneous IHs are those with multiple or multifocal cutaneous IHs. Because studies have documented that infants with multiple cutaneous IHs are at increased risk of having hepatic involvement, screening for hepatic lesions with abdominal ultrasonography has been suggested for infants with 5 or more cutaneous IHs. Other nonhepatic visceral organ involvement is relatively rare in infants with multiple cutaneous IHs; however, performing a thorough review of systems and physical examination on any infant with multiple cutaneous hemangiomas is advisable.

Infants with hepatic IHs may remain clinically asymptomatic or can present with life-threatening symptoms of congestive heart failure, hepatomegaly, or abdominal distension. Hepatic IHs have been characterized as occurring in 3 patterns: focal, multifocal, and diffuse. Focal singular lesions are usually detected on antenatal imaging or as an abdominal mass in the newborn infant. It is now clear that these lesions are not true IHs; rather, they are the hepatic manifestation of a RICH, which explains why they are fully grown at birth. They spontaneously involute 90% volumetrically by 13 months of age, and involution is not likely to be hastened by pharmacologic agents. Diagnosis may be made by ultrasonography on the basis of the presence of arteriovenous shunting or on CT or MRI, which reveal hyperintense peripheral contrast enhancement and central sparing. Some hepatic RICHs have associated macrovascular shunts (usually hepatic artery to hepatic vein) that can cause high-output cardiac failure. If shunts are absent, a hepatic RICH can be observed with serial ultrasonography to determine whether its behavior is typical. Differential diagnosis can include hepatoblastoma and mesenchymal hamartoma. If imaging and involution are not diagnostic, percutaneous biopsy may be indicated. If shunts are present and causing high-output failure, selective embolization can ameliorate cardiac failure, and the lesion can be allowed to involute. There is a very small risk of rupture and hemorrhage with extremely large tumors. Surgical resection or transplantation is rarely necessary.

Multifocal and diffuse hepatic IHs exist on a spectrum. They are true IHs and often coexist with cutaneous lesions. In a prospective study in 151 infants, 16% of infants with 5 or more cutaneous IHs were found to have hepatic lesions on screening ultrasonography. Multifocal lesions have ample normal hepatic parenchyma between them.
are often asymptomatic; however, some patients will have macrovascular shunting causing high-flow and possible high-output cardiac failure. These patients are best treated pharmacologically with propranolol or corticosteroids. Shunts will usually close with involution of the IH. Selective shunt embolization is a consideration in those rare instances in which rapid cardiac failure does not allow sufficient time for response to pharmacotherapy.

Diffuse lesions have little hepatic parenchyma apparent between densely packed nodular IHs throughout the liver. Patients present with hepatomegaly, which can become massive. They may develop abdominal compartment syndrome with compromised ventilation, renal failure attributable to renal vein compression, or poor inferior vena caval blood return to the heart and may progress to death. Virtually all diffuse hepatic IHs cause acquired hypothyroidism attributable to the inactivation of thyroid hormones by type 3 iodothyronine deiodinase constituent in the lesions. Hypothyroidism can be very profound and can require massive replacement hormone dosing. Multifocal lesions also suggest the need for prompt thyroid screening, because they may collectively contain enough tumor mass to overwhelm endogenous thyroid production.

Infants with diffuse hepatic IH, particularly those with congestive heart failure, are at greatest risk of mortality. Aggressive pharmacologic therapy and thyroid hormone replacement are indicated for infants with such lesions. Effective IH treatment will result in a gradual reduction in the requirement for thyroid replacement and eventual return to the euthyroid state. High-flow shunts are uncommon in diffuse lesions. There is no role for embolization in the absence of macrovascular shunts and a high-output state. An infant who presents with massive hepatomegaly and abdominal compartment syndrome occasionally has disease that cannot wait for drug-induced involution; in rare cases, such a child may be a candidate for hepatic transplantation.

CONCLUSIONS
The management of IHs has evolved considerably in the past decade. The serendipitous discovery of the response of IH to systemic β-blockers has expanded therapeutic options for these tumors. Timolol, a topical β-blocker, has shown promise as a potential therapy for superficial lesions. A greater understanding of the indications and limitations of laser therapy also has emerged. Concurrently, bench research has provided a deeper understanding of the origins of IH and patterns of IH growth. It is anticipated that continued research will further clarify the etiology of IH, hopefully leading to pathogenesis-directed therapeutic options.

Although many IHs can be observed without treatment, others will clearly benefit from medical or surgical intervention. It is important for pediatricians to keep abreast of advances in IH management, because the types of intervention and the threshold for their use are likely to evolve. When complications are likely or the threshold for intervention is uncertain, referral to an experienced specialist or a multidisciplinary vascular anomalies center may be advantageous.

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ABBREVIATIONS

bFGF: basic fibroblast growth factor
CT: computed tomography
EPC: endothelial progenitor cell
GLUT1: glucose transporter protein isoform 1
HemSC: multipotential stem cell derived from IH specimens
IH: infantile hemangioma
IL: interleukin
KHE: kaposiform hemangioendothelioma
KMP: Kasabach-Merritt phenomenon
LBW: low birth weight
LUMBAR: Lower body IH and other cutaneous defects, Urogenital anomalies and ulceration, Myelopathy, Bony deformities, Anorectal malformations and arterial anomalies and Renal anomalies
MMP: matrix metalloprotease
PDL: pulsed-dye laser
PHACE: Posterior fossa defects, Hemangiomas, cerebrovascular Arterial anomalies, Cardiovascular anomalies including coarctation of the aorta, and Eye anomalies
MRA: magnetic resonance angiography
NICH: noninvoluting congenital hemangioma
RICH: rapidly involuting congenital hemangioma
TA: tufted angioma
VEGF: vascular endothelial growth factor

REFERENCES


20. Pratt AG. Birthmarks in infants. AMA Arch Derm Syphilol. 1953;67(3):302–305


64. North PE, Waner M, Mizeracki A, et al. A unique microvascular phenotype shared by juvenile hemangiomas and


112. Frank RC, Cowan BJ, Harrop AR, Astle WF, McPhalen DF. Visual development in infants: visual complications of


194. Oranje AP, Janmohamed SR, Madern GC, de Laat PC. Treatment of small superficial hemangioma with timolol 0.5% ophthalmic solution: a series of 20 cases. Dermatology. 2011;223(4):752


275. Scheepers JH, Quaba AA. Does the pulsed tunable dye laser have a role in the management of infantile haemangiomas? Observations based on 3 years’ experience. *Plast Reconstr Surg.* 1995;95(2):305–312


Available at: www.pediatrics.org/cgi/content/full/128/5/1053


307. Cogen MS, Elsas FJ. Eyelid depigmentation following corticosteroid injection for infantile ocular adnexal hemangioma. *J Pediatr*


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