Quick Reference Guide

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Diagnosis and Management of Infantile Hemangioma

QUICK REFERENCE GUIDE

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 develops 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.

In the AAP Clinical Report, “Diagnosis and Management of Infantile Hemangioma,” individuals from the many specialties involved in the treatment of IH provide such guidance for the primary care provider. It is the purpose of this guide 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.

*DARROW DH, GREENE AK, MANCINI AJ, NOPPER AJ.  DIAGNOSIS AND MANAGEMENT OF INFANTILE HEMANGIOMA. SECTION ON DERMATOLOGY, SECTION ON OTOLARYNGOLOGY–HEAD AND NECK SURGERY, AND SECTION ON PLASTIC SURGERY.

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01.

Nomenclature

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Nomenclature

IH ARE TRUE TUMORS THAT HAVE THE UNIQUE ABILITY TO INVOLUTE AFTER PROLIFERATION

Vascular Anomalies

<table>
<thead>
<tr>
<th>Vascular Tumors</th>
<th>Vascular Malformations</th>
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<tbody>
<tr>
<td>Benign</td>
<td>Capillary</td>
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<tr>
<td>Infantile Hemangioma</td>
<td>Venous</td>
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<tr>
<td>Congenital</td>
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<tr>
<td>Rapidly Involuting</td>
<td>Arteriovenous</td>
</tr>
<tr>
<td>Non-involuting</td>
<td>Complex</td>
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<tr>
<td>Partially Involuting</td>
<td>(Combination associated anomalies)</td>
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<tr>
<td>Pyogenic Granuloma</td>
<td></td>
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<td>Others</td>
<td></td>
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</table>

- Port Wine Stain/Capillary Vascular Malformation
- Venous Malformation
- Lymphatic Malformation
- Arteriovenous
- Complex (Combination associated anomalies)
IH IMPOSTERS INCLUDE:

**Congenital Hemangiomas**
are biologically and behaviorally distinct from IH.

**Pyogenic Granuloma**
may be misdiagnosed as IH and is more accurately categorized as a hyperplasia rather than a true neoplasm.

**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 2 other vascular neoplasms, kaposiform hemangioendothelioma (KHE) and tufted angioma (TA).
Epidemiology

THE INCIDENCE OF IH IN THE GENERAL POPULATION IS APPROXIMATELY 5%.

- Risk factors for IH include being white, being female, and having low birth weight.

- Associations are also reported with older maternal age, multiple gestation births, placenta previa, pre-eclampsia, use of fertility drugs or erythropoietin, breech presentation, and being the first born.
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Basic Science

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IH in proliferative phase.
Pathogenesis

IHs 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 placenta-like tissues.

Histopathology

• Composed of endothelial cells and pericytes

• Late stage proliferating IH are characterized by fibrous septae which divide masses of endothelial cells. Large feeding and draining vessels may be noted within the septae.

• Biopsy is not usually necessary unless the clinical picture is not typical of IH.

• Proliferating IH are well circumscribed and lack a capsule.

• Involuting IH are fibrofatty and less defined.

• Characterized by a few residual vessels and fibrofatty tissue.

• Glucose transporter protein isoform 1 (GLUT1) is a commonly used immunochemical marker for IH.

• Other placental vascular markers may be present as well. None of these markers are present in vascular malformation or other infantile tumors.
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Clinical Behavior

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## Phases of Growth

### 0-1 month
IHs usually make their initial appearance prior to 4 weeks of age and often within the first 2 weeks of life. The most rapid growth may occur between 2 and 8 weeks of age.

### 3-4 months
IHs complete most of their growth by 3-4 months of age.

### 12 months
Involution of IHs begins between 6 and 12 months of age but may be delayed in those IH which are primarily subcutaneous.

### 4 years
In most cases, the majority of involution is completed by age 4.
IHs can be characterized by depth in the skin: superficial, deep, or combined which is most common.

Morphologically IHs are defined as focal (often round or oval), multifocal (more than one focal lesion), or segmental (usually large and with a distinctive embryologic pattern).

Superficial IHs appear earlier and begin involution sooner than their deeper counterparts.

Segmental IHs are more commonly associated with complications.

The presence of more than 5 focal IHs may be associated with a higher risk of hepatic hemangiomas.

Clinical Appearance
Complications

SEGMENTAL IHs are far more likely than focal IHs to result in a complication, usually ulceration.

FOCAL IHs cause complications primarily by virtue of their location on or near vital structures.

FACIAL IHs cause complications more frequently than nonfacial IHs and are several times more likely to receive some form of therapy.

• MINOR BLEEDING from an ulcerated IH is common, but rarely of clinical significance; bleeding from a nonulcerated IH is rare.

• Patients with extensive IH in the "BEARD" DISTRIBUTION are more likely to have involvement of the airway.

• High risk PERIOCULAR IHs are those that are larger than 1 cm in diameter, located near the nose, associated with ptosis or eyelid margin change, or displacing the globe.

• Diffuse IH OF THE LIVER may be associated with severe consumptive hypothyroidism.

The presence of multiple IHs in the "beard" distribution is associated with a higher likelihood of airway involvement (reproduced with permission from J Pediatr. 1997;131(4):643–646 ©Elsevier).

Patient with airway involvement requiring tracheotomy is shown with "beard" involvement at the lip and chin (B) as well as the parotid area and neck (C).
Syndromes & Associations

The hallmark of PHACE (Posterior Fossa, Hemangioma, Arterial, Cardiac, Eyes) 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 (Lower body hemangioma) and other cutaneous defects, Urogenital anomalies, Ulceration, Myelopathy, Bony deformities, Anorectal malformations, Arterial anomalies, and Renal anomalies 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.

For more info, click here
05. Imaging

IMAGING OF IH IS NOT USUALLY NECESSARY, BUT IMAGING MAY BE REQUIRED WHEN:

- The diagnosis is uncertain
- Evaluation of extent is necessary particularly when associated with functional impairment or risk of hepatic or other organ involvement
- The IH is a possible marker of PHACE or LUMBAR syndrome
- Response to therapy needs to be monitored
06.

Treatment

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Indications for IH Intervention

THE INDICATIONS FOR INTERVENTION FOR IH INCLUDE:

- Urgent treatment of existing or imminent functional impairment, pain, or bleeding.
- Evaluation to identify structural anomalies potentially associated with IH.
- 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:

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
8. Physician experience
Management of ulcerated IH consists primarily of:

**ADJUVANT THERAPIES MAY INCLUDE:**

- Topical agents including antibiotics, anesthetics, or wound dressings
- Pulsed dye laser
- Short course of oral steroids especially for ulcerated IH
Propranolol, administered orally at a dose of 1 to 3.4 mg/kg/day, is efficacious in reducing size and discoloration of IH.

The mechanism of propranolol’s effect on IH likely involves several processes including vasoconstriction, inhibition of angiogenesis, and stimulation of apoptosis.

Propranolol has largely supplanted corticosteroids in the management of IH due to side effects associated with the latter. Intralesional steroids may still be useful in managing bulky focal IHs.

When propranolol is initiated in the office setting, heart rate and blood pressure are determined at baseline, 1, and 2 hours after the first dose of propranolol, and 1 and 2 hours after each dosage increases. As an alternative pulse rate checks before and 1-2 hours after increases in dose can be performed by parents at home.

Administration of propranolol with feedings, and holding doses if oral intake is compromised, reduces the likelihood of hypoglycemia.

COMMON SIDE EFFECTS
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.

Application of topical timolol has demonstrated efficacy in the management of superficial IHs.
Laser Therapy

**MOST USEFUL IN THE TREATMENT OF NONPROLIFERATING SUPERFICIAL LESIONS**

- Laser treatment of IH may be useful in early nonproliferating 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.

- For Nd:YAG laser may be useful for treatment of residual deep seated vessels.

Surgical Therapy

**INDICATIONS FOR SURGERY FOR IH DURING INFANCY ARE LIMITED TO:**

- Failure of, or contraindication to, pharmacotherapy

- Focal involvement in an area anatomically favorable for resection

- 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 3 years because, by this age, self-esteem and long-term memory begin to form and the tumor has completed most of its involution.
07. Special Anatomic Concerns

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Periocular IH

IHS OF THE PERIOCULAR AREA

Periocular IHs have the potential to cause compression of the globe, obstruction of the visual axis, and extension into the retrobulbar space, resulting in refractive errors, strabismus, and amblyopia, leading to vision loss.

The permanence of ophthalmic complications due to IH is often related to their severity and duration, underscoring the need for early ophthalmologic evaluation.

IH of the left eye causing visual field cut and astigmatism. Untreated, the lesion could proliferate, potentially resulting in deprivation amblyopia.
HEPATIC IHS HAVE BEEN CHARACTERIZED AS OCCURRING IN 3 PATTERNS:

**Focal**
Focal hepatic IHs are most commonly the hepatic manifestation of rapidly involuting congenital hemangioma (RICH); they are fully grown at birth, and involution is almost complete by 1 year of age.

**Multifocal**
Multifocal hepatic IH have normal hepatic parenchyma between them. Many patients are asymptomatic; however, those with high-flow and/or high-output cardiac failure require pharmacologic therapy with propranolol or corticosteroid. Patients with diffuse hepatic IHs present with hepatomegaly that can lead to compromised ventilation, renal failure attributable to renal vein compression, poor inferior vena caval blood return to the heart, and death.

**Diffuse**
Diffuse hepatic IHs may cause acquired hypothyroidism. Most hepatic IHs are managed medically; rarely embolization, surgical resection, and transplantation have been necessary.

MULTIFOCAL AND DIFFUSE HEPATIC IHS ARE TRUE IHS AND OFTEN COEXIST WITH CUTANEOUS LESIONS.

An hepatic ultrasound should be considered when multiple cutaneous IHs are present and a full abdominal examination including palpation of the liver and spleen should be performed to exclude organomegaly which can be associated with hepatic involvement.
Other Anatomic Areas of Concern

**AIRWAY**

Most patients with IHs of the airway have subglottic involvement causing biphasic stridor and barking cough, often mistaken as croup. Voice and swallowing are generally normal.

Diagnosis of airway IHs is usually made by endoscopy in the operating room or by the bedside. In most cases, IHs of the airway may be managed medically; in cases of severe obstruction, surgical reduction or excision may be entertained.

**NASAL TIP**

Early management of nasal tip IH reduces the likelihood of poor cosmesis resulting from skin excision and/or replacement and effects on the underlying cartilage.

Goals of surgery for nasal tip IHs include complete IH excision, reconstruction of the cartilaginous framework, and judicious skin excision and redraping.

**LIP**

IHs involving the lips and perineum have a tendency to ulcerate, and these regions are difficult to reconstruct. Such lesions are appropriately managed aggressively with medical therapy.

Although these are common locations for IH, they are not the only locations. Be aware that IH can occur anywhere.