# Guidelines for the Treatment of Infantile Hemangiomas: A Position Paper from the Israeli Association of Dermatology and Venereology

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**ABSTRACT** Infantile hemangioma (IH) is the most common benign vascular tumor in infancy. Recent advances, particularly in beta-blocker therapy, have significantly improved the management of IHs. Early identification and treatment of IH may help reduce morbidity and associated complications. In this review, experts in pediatric dermatology in Israel who have experience in treating IH, formulated national guidelines for the diagnosis and treatment of IHs, providing evidence-based recommendations for selecting appropriate therapeutic approaches. These Israeli national guidelines provide a structured approach to the diagnosis and treatment of IH, emphasizing early referral, appropriate treatment selection, and careful monitoring. The guidelines serve as a critical resource for pediatricians and dermatologists, ensuring optimal patient outcomes while minimizing complications.

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**KEY WORDS:** beta-blockers, infantile hemangiomas, national guidelines, monitoring

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Infantile hemangioma (IH) is the most common benign vascular tumor in infancy, affecting 4–10% of newborns. It is more frequent in girls (3:1), premature infants, low birth weight babies, multiple gestations, and cases with placental abnormalities [1].

While its pathogenesis is not fully understood, IH is thought to result from an abnormal pluripotent stem cell response to hypoxic insults, as well as to other factors responsible for the proliferation of endothelial cells [1,2].

IH typically appears after birth and follows three phases: the proliferative phase with rapid growth in the first 3–5 months, the plateau phase that is stable until 9–12 months, and the involution phase with gradual regression from age 1 to 3–4 years. Approximately half of the cases leave residual skin changes. Most IHs resolve without complications or treatment, but early intervention is recommended when cosmetic, functional, or medical concerns arise. In these cases, infants should be referred for treatment as soon as possible [3].

Advances in IH research have highlighted the role of beta-blockers in the treatment of IHs as well as a growing awareness of both complications and the impact of hemangiomas on quality of life [3,4].

We proposed guidelines for selecting a tailored treatment for hemangiomas through a review of the scientific literature on the topic and the formulation of recommendations by an expert consensus.

## METHODS

Fifteen experts in the field of pediatric dermatology with clinical experience in treating IHs, members of the Israeli Pediatric Dermatology Society, and members of the Israeli Association of Dermatology and Venereology convened in a series of meetings to develop the guidelines. We reviewed scientific literature based on PubMed and other database searches. We used relevant keywords including *beta-blockers*, *monitoring*, *international guidelines*, and *infantile hemangioma*. The committee focused on definitions, topical and oral treatments with beta-blockers, contraindications to treatment, and other treatment modalities.

Based on the literature review and clinical experience, we developed guidelines that were discussed within the expert group and sent to the committee members for approval.

## RESULTS

### *Definitions*

IHs can be classified according to their depth as superficial, deep, or mixed. [Table1]. Additional classifications related to their distribution include localized hemangioma, segmental hemangioma, undefined hemangioma, and multifocal hemangiomas. IH with minimal or arrested growth (IH-MAG) refers to IHs that appear at presentation as telangiectatic patches with minimal or no growth beyond that stage [1].

IHs may be isolated or a part of a syndrome. Syndromes involving IHs include PHACE syndrome (Posterior fossa anomalies; Hemangioma; Arterial anomalies; Cardiac anomalies; Eye anomalies); LUMBAR syndrome, also referred to as PELVIS/SACRAL syndrome (lower-body hemangioma and other cutaneous defects, urogenital anomalies, ulceration, myelopathy, bony deformities, anorectal malformations, arterial anomalies, and renal anomalies); beard hemangiomas; and multifocal hemangiomas [1,5]. Syndromes, special cases of IHs, and recommended investigations are shown in Table 1.

### DIFFERENTIAL DIAGNOSIS

Although superficial IHs are easy to diagnose, some cases of deep or mixed IHs or atypical presentations pose a diagnostic dilemma [1,6].

A differential diagnosis for IH can encompass benign lesions such as capillary or vascular malformations, congenital hemangiomas, locally aggressive lesions such as tufted angiomas, kaposiform hemangioendothelioma, or malignant tumors [6]. An alternate diagnosis for infantile hemangioma should be considered when the lesion has atypical

**Table 1.** Syndromes and special cases of infantile hemangiomas and recommended investigations

| Syndrome | Distribution | Definition/association | Investigation |
|---|---|---|---|
| **PHACE syndrome** | Segmental > 5 cm on the head/neck; or < 5 cm with additional finding* | Posterior fossa anomalies, hemangioma, arterial anomalies, cardiac anomalies, eye anomalies; may have sternal defects | Ophthalmologist, neurologist, cardiologist, echocardiography, MRI/MRA head and neck |
| **LUMBAR syndrome** | Lumbar /sacral area, lower limbs | Lower-body hemangioma and other cutaneous defects; urogenital anomalies; ulceration; myelopathy; bony deformities; anorectal malformations; arterial anomalies; and renal anomalies; associated with spinal dysraphism | MRI spine, pelvis, and kidneys |
| **Beard hemangioma** | A segmental facial hemangioma on the chin and mandibular area | Associated with subglottic IH, may be associated with PHACE syndrome | ENT, optic fiber; or pulmonologist, bronchoscopy |
| **Multifocal hemangiomas** | Defined as having 5 or more hemangiomas (any location) on the skin | Associated with liver hemangioma; associated lung, gastrointestinal, brain hemangiomas (rare) | Ultrasound of liver; in additional symptoms, head ultrasound, chest X-ray, gastroenterology exam |
| **Periorbital IH** | Periorbital location | Risk for ptosis, strabismus, amblyopia, or astigmatism | Ophthalmologist |
| **Symptomatic IH**** | Large IH, or internal location; liver hemangioma | Risk for heart failure, hemodynamic compromise, consumptive hypothyroidism | Echocardiography, abdominal ultrasound, thyroid function testing (TSH, FT3, FT4) |

ENT = ear-nose-throat, IH = infantile hemangioma, MRA = magnetic resonance angiography, MRI = magnetic resonance imaging, PHACE = posterior fossa anomalies, hemangioma, arterial anomalies, cardiac anomalies, eye anomalies

*Ventral defects, aortic coarctation

**symptoms may include tachypnea, fatigue, distended abdomen

features, such as late onset, firmness, hemorrhagic components, vesicles, a bruit on auscultation, or unexplained pain. An unusual growth pattern or lack of response to standard treatment also warrants further evaluation [7,8].

Diagnostic tools include ultrasonography (with Doppler imaging), magnetic resonance imaging (MRI) or angiography for vascular assessment, biopsy for histological examination, and immunohistochemical testing for glucose transporter 1 (GLUT-1), a key marker distinguishing hemangioma from other vascular anomalies [1,7].

## INDICATIONS FOR REFERRAL

The main indications for referring patients to a specialist are as follows: life-threatening hemangiomas, risk of functional impairment, ulceration, associated structural anomalies or disfigurement, aesthetic impairment, or scarring [5,9] [Table 2].

To assist in determining the need for referrals, the Infantile Hemangioma Referral Score form (IHReS) may be used. IHReS is a validated scoring tool developed by expert committees, aimed at improving decision-making among healthcare professionals regarding the referral of infants with infantile hemangioma [10].

## SYSTEMIC TREATMENT

The first-line treatment for infantile hemangiomas requiring intervention is systemic beta-blocker therapy. This treatment has replaced the previous treatment of choice, which was systemic corticosteroids [9,11].

Two therapeutic options are available in Israel:

- Propranolol is a non-selective antagonist of the β1 and β2 adrenergic receptors [4]. Propranolol hydrochloride for systemic use (Hemangiol®, Padagis, Israel) was approved for this indication by the U.S. Food and Drug Administration in March 2014. The treatment was approved for use by the Israeli Ministry of Health in June 2017 and was included in the national health basket in January 2020.
- Atenolol is a selective antagonist of the β1 adrenergic receptor, with minimal effect on the β2 receptor [12]. Atenolol is not registered for the treatment of IH and is therefore used off-label.

Possible side effects of systemic beta-blockers are provided in Table 3 [4,9,13]. Parents should be advised about the potential side effects, with an emphasis that serious adverse effects are extremely rare. Contraindications for beta-blocker treatment include hypersensitivity

**Table 2.** Indications for referral to treatment of infantile hemangiomas

| Indication | Hemangioma type | Risk |
|---|---|---|
| **Life-threatening hemangiomas** | Actively bleeding | Anemia, hemodynamic compromise |
| | Symptomatic IH | Heart failure, hemodynamic compromise |
| **Functional impairment** | Laryngeal IH | Airway obstruction |
| | Periocular IH | Ptosis, strabismus, amblyopia, or astigmatism |
| | Lips, oral cavity | Feeding impairment |
| | Fingers and toes | Finger mobility |
| **Ulceration** | Segmental IHs; IHs located on the lips, columella, in intertriginous areas (e.g., neck, axillae, inguinal region), helix of ear, gluteal cleft, perineum or perianal area | Pain, bleeding, infection, and scarring, which may result in aesthetic impairment |
| **Associated structural anomalies and disfigurement** | Segmental IH | Ulceration |
| | Segmental IH of face | PHACE syndrome |
| | Segmental IH of lumbosacral | LUMBAR syndrome |
| | Segmental IH of face, trunk; IH on an extremity > 2 cm, or thick superficial IH (2 mm) | High risk of scarring and/or permanent disfigurement |
| | IH of tip of nose, lips, parotid gland | |
| | IH of scalp > 2 cm | Permanent alopecia, profuse bleeding |
| | IH of breast in females | Permanent changes in breast development (e.g., breast asymmetry) or nipple contour |

IH = infantile hemangioma, PHACE = posterior fossa anomalies, hemangioma, arterial anomalies, cardiac anomalies, eye anomalies

to the medication, certain cardiac and respiratory conditions (i.e. bradycardia, uncontrolled asthma) or hypoglycemia predisposition [11,14].

Evidence has dispelled earlier concerns about neurodevelopmental effects in infants and young children treated with beta-blockers [14].

### TREATMENT WITH PROPRANOLOL VERSUS ATENOLOL

Propranolol has been studied extensively since its first discovery in 2008. It remains the only medication assessed in a randomized controlled study [4,9,13,14]. Propranolol hydrochloride is currently the only medication approved by U.S. regulatory authorities and Israeli Ministry of Health for IHs.

Due to atenolol's selective mechanism of action and its reduced penetration of the blood–brain barrier, its use is associated with fewer respiratory and neurological side effects compared to propranolol, specifically, a lower rate of bronchial hyperreactivity, agitation, and sleep disturbances [15]. In addition, with a longer terminal half-life of 6 to 8 hours (versus propranolol's 3 to 6 hours), atenolol has the advantage of once-daily treatment [12,14].

**THE ISRAELI NATIONAL GUIDELINES FOR THE TREATMENT OF INFANTILE HEMANGIOMAS PROVIDE A PRACTICAL, EVIDENCE-BASED FRAMEWORK ADAPTED TO LOCAL HEALTHCARE SETTINGS.**

**Table 3.** Possible side effects of systemic beta-blocker medications

| System | Adverse effect (frequency%) |
|---|---|
| Gastrointestinal | Vomiting (< 10%), diarrhea (< 10%), constipation (1–10%), anorexia, nausea |
| Neurological | Sleep disturbances (< 10%), nightmares, fatigue (1–10%), agitation (1–10%) |
| Respiratory | Bronchitis (< 10%), bronchospasm (1–10%), bronchiolitis (1–10%), dyspnea, wheezing, bronchial hyperreactivity |
| Hemodynamic effects | Cold extremities and limb cyanosis (1–10%); hypotension (1–10%), bradycardia (< 0.1%), AV block (< 0.1%) |
| Endocrinology | Hypoglycemia (< 0.1%) |

### TOPICAL TREATMENT

In Israel, there are two therapeutic options. Propranolol gel is a compounded preparation formulated at concentrations of 4–8%. It is applied topically as a thin layer twice daily [16]. Timolol gel-forming drops are prescribed at a concentration of 0.5% and applied topically to the skin, in contrast to their original indication as eye drops. The dosing for timolol drops is one to two drops, twice daily [17].

Although these topical treatments are not registered for the treatment of IH, they are frequently prescribed off-label, with established evidence supporting their effectiveness [16,17].

### INDICATIONS FOR TOPICALTREATMENT

Topical treatment is indicated for superficial, thin hemangioma that is raised ≤ 1–2 mm above the skin surface, with a size of up to 5 cm [18]. This treatment may also be recommended in cases where there is a contraindication to oral treatment and/or as adjunctive treatment after oral beta-blocker therapy [17,19].

### POSSIBLE SIDE EFFECTS

Possible side effects include hypersensitivity to the formulation, manifesting as a rash at the application site requiring discontinuation of therapy and initiation of a topical corticosteroid. Rarely, systemic side effects have been reported, suggesting the possibility of systemic absorption, particularly in ulcerated hemangiomas [20].

Topical therapies do not require dedicated safety monitoring. Routine followup for therapeutic efficacy is sufficient.

### ALTERNATIVE PHARMACOLOGICAL TREATMENTS

Alternative treatments should be considered if beta-blockers are contraindicated or cause significant side effects. Intralesional corticosteroids may be used as an additive treatment for small bulky lesions (e.g., lips or nose) [3,14]. Corticosteroids (prednisone/prednisolone) are dosed at 2–5 mg/kg per day for 4–12 weeks, with gradual tapering until 9–12 months of age. Sirolimus (rapamycin) may be effective for treatment-resistant hemangiomas, particularly with internal organ involvement.

High dose corticosteroids and sirolimus carry a substantial risk of severe adverse events and should be limited for specialized cases under close supervision [21]. Nadolol, a non-selective beta-blocker, is an alternative for patients who cannot tolerate other beta-blockers, although it is rarely used in Israel [14,22].

### OPTIMAL TIMING FOR TREATMENT INITIATION

There is a window of opportunity to treat complicated IHs. Lesions that are potentially high risk should be referred to for treatment as early as possible, optimally by 1 month of age [9]. IHs referred during the proliferative

phase are associated with improved therapeutic outcomes; however, intervention can still be beneficial in later stages [9,19].

### PRE-TREATMENT ASSESSMENT

The initiation of systemic beta-blocker therapy should be conducted in consultation with a pediatric dermatologist or a specialist experienced in treating pediatric vascular tumors [9,11]. The assessment should include medical history and physical examination. An electrocardiogram is indicated for infants with a low heart rate for their age, suspected arrhythmias, a family history of congenital heart disease, or maternal history of connective tissue disease. In these cases, a consultation with a cardiologist is advised [9,11].

### TREATMENT INITIATION FRAMEWORK

In healthy infants aged 5 weeks or older, and preterm infants with a corrected age of 5 weeks and a minimal weight of 4.5 kg, treatment can be started in a day hospitalization or specialized outpatient setting under the supervision of an experienced clinician in IH management [23].

Hospitalization is recommended in the following cases: Infants under 5 weeks of age, infants of any age with inadequate social support or infants of any age with cardiovascular or respiratory disorders, major syndromic involvement, or conditions affecting glucose balance [5,24].

### INITIAL TREATMENT DOSAGE

Propranolol is given at an initial dose of 1 mg/kg/day divided into two doses. After one week, the dose is increased to 2 mg/kg/day divided into two doses. The maximum dose is 3 mg/kg/day divided into two doses. The doses should be given at least 9 hours apart [25,26]. Atenolol is given at an initial dose of 1 mg/kg once daily, with a maximum dose of 2–3 mg/kg/day,

For ulcerating hemangiomas or PHACE syndrome, the initial dose is 0.5 mg/kg with gradual 0.5 mg/kg bet-blocker medication dose escalation as appropriate [5]. This dose is given to prevent vasoconstriction and associated complications (i.e., arterio-occlusive events, necrosis). In PHACE syndrome the beta-blocker should be given in three divided doses to minimize changes in blood pressure [9].

### MONITORING DURING TREATMENT INITIATION

Blood pressure and heart rate should be recorded before the first dose, re-evaluated 1–3 hours later, and reassessed after every 0.5 mg/kg/day dose escalation [9,11].

Glucose monitoring is not required [9]. To reduce the risk of hypoglycemia, parents should be instructed to administer the medication (propranolol or atenolol) immediately after feeding. If the child reduces food intake (e.g., due to illness), the medication should be withheld until normal feeding resumes. In addition, if the child spits out or vomits the medication, a repeated dose should not be given [8,9]. While on systemic treatment, the infant's vaccination plan should remain unchanged.

### ONGOING TREATMENT MONITORING

During beta-blocker therapy, routine follow-up with a pediatrician or well-baby clinic is recommended. Monitoring should include pulse and blood pressure monitoring, which can be performed during clinic visits. Some experts suggest that blood pressure and heart rate monitoring beyond the initial treatment phase is unnecessary [9,27].

Dose adjustments (beyond weight-based modifications) and medication alteration when needed, should be made by a pediatric dermatologist or a vascular lesions specialist [9].

### DURATION OF TREATMENT

The standard duration of beta-blocker treatment is at least 6 months, typically continuing until 12–15 months of age. In some cases, extended treatment may be considered based on clinical judgment, particularly for hemangiomas with an elevated risk of recurrence or those that have not achieved optimal therapeutic response. If treatment is initiated during the regression phase (after the proliferative phase), it should continue until stable improvement is achieved, as determined by clinical assessment [19,28].

### TREATMENT DISCONTINUATION

Discontinuation of treatment is determined by the treating physician and based on clinical evaluation, when the hemangioma has stabilized or regressed; when it has shown improvement in color and volume, with minimal redness, residual telangiectasia, skin thickening, or swelling, and without functional impairment.

If the hemangioma has fully regressed, treatment should continue for at least 6 months from treatment start or until the child reaches 12 months of age [4,14]. Tapering (gradual dose reduction) is not required [9].

The guidelines for treatment initiation, monitoring, and discontinuation are summarized in Table 4.

### RISK OF RECURRENCE

Recurrence occurs in 10–25% of cases and is more common if treatment is discontinued before 12 months of age, and especially before 9 months. Recurrence risk is higher in mixed, deep, or segmental hemangiomas; lip hemangi-

omas; and in female infants. Recurrence may occur from the end of beta-blocker treatment up to 6 months after discontinuation [28].

### RECURRENCE MANAGEMENT

If hemangioma recurrence occurs (i.e., redness or volume increase), treatment should be resumed at the previous effective dose based on clinical assessment. In mild recurrence cases, topical beta-blockers (timolol drops or propranolol gel) may be considered. Observation may be advised and parents informed that spontaneous regression may be expected [29].

### ADDITIONAL TREATMENTS

Additional treatments for hemangiomas include surgery and laser therapy. Surgery is mainly indicated to correct residual changes such as scars or excess fibro-fatty tissue. It is typically performed at ages 3 to 5 years when the hemangioma is smaller and less vascularized. However, earlier intervention may be necessary for ulcerated or functionally impairing hemangiomas if medical treatment fails. Laser therapy, particularly pulse dye laser (PDL) at 595 nm, is effective in treating superficial residual changes, while Nd: YAG at 1064 nm may help with deeper lesions. The combination of laser therapy with beta-blockers during the proliferative or ulcerated stages of hemangiomas is still under investigation [3,14].

## DISCUSSION

The purpose of the Israeli national guidelines for the treatment of IHs is to facilitate early intervention, prevent complications, and clarify treatment options and key considerations of treatments. Identification of hemangiomas can be performed by a pediatrician or dermatologist, but treatment should ideally be managed by a pediatric dermatologist or a physician specializing in vascular tumors. While there is a general consensus on treatment indications [Table 2], duration, and follow-up [Table 4], these recommendations are not absolute, and clinical judgment remains essential in daily practice.

The position paper considers the available medications in Israel, specifically systemic treatments with propranolol or atenolol, and topical treatments with timolol drops or propranolol gel. It also addresses the setting for initial dose administration and the follow-up of treated patients, which varies between providers and medical centers.

The Israeli national guidelines align with European [8,11], American [9], and Australian [30] recommendations with some modifications, covering all available

**Table 4.** Summary of recommendations for treatment initiation, monitoring, and post-treatment follow-up for treatment of infantile hemangiomas

| Time period / Intervention | Pretreatment | Initiation | Follow-up | After cessation |
|---|---|---|---|---|
| **Clinical visit** | ✔ | Day-hospitalization; or clinic with supervision* | Every 1–3 months, in clinic or via telemedicine | If residual changes, yearly until age 3–5 years |
| **Electrocardiogram** | When indicated** | – | – | – |
| **Weight** | ✔ | ✔ | ✔ | – |
| **Blood pressure** | ✔ | After 1–3 hours | On major dose escalation$^{\Delta}$ | – |
| **Heart rate** | ✔ | After 1–3 hours | On major dose escalation$^{\Delta}$ | – |
| **Dose** | Give prescription: propranolol 1 mg/kgl divided into 2 doses, twice daily | Propranolol: give 0.5 mg/kg under supervision, second dose 0.5 mg/kg after 9 hours (at home), continue twice daily | Propranolol: week 2: 2 mg/kg increase up to 3 mg/kg max | No taper needed |
| | OR | | | |
| | Atenolol 1 mg/kg, once daily | Atenolol 1 mg/kg, once under supervision, continue once daily | Atenolol increase up to 2–3 mg/kg as needed | |
| **Additional intervention** | Check the medication formulation and instruct the parents of the correct dose | Thorough explanation of medication administration, possible adverse effects, and signs of concern*** | Remind parents of possible concerns, may add laser treatment | May continue topical propranolol or timolol by clinical judgment, laser or surgery if needed, starting at age 3–4 years |

*Hospitalization only in specific cases <5 weeks of age, low social support, medical morbidity
**Indicated for infants with a low heart rate for their age, suspected arrhythmias, a family history of congenital heart disease, or maternal history of connective tissue disease; may consult a cardiologist
***Signs of concern: lethargy, convulsions, shortness of breath, behavioral changes
$^{\Delta}$Dose escalation > 0.5 mg/kg

treatment options, and monitoring schedules, as agreed upon by the committee members.

## CONCLUSIONS

The guidelines for the treatment of IHs serve as a valuable resource for pediatricians and dermatologists in identifying, diagnosing, referring, and managing these lesions. Early referrals are crucial to prevent complications such as deformities, scarring, and damage to vital structures.

Pharmacological treatment plays a key role in halting hemangioma growth and promoting early regression. When managed under the supervision of a pediatric dermatologist, this therapy is both effective and safe for infants.

Ultimately, these guidelines provide essential support for physicians treating infants and children with hemangiomas. However, they do not replace specialist evaluation or individualized clinical judgment, which should always guide patient care.

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