INFANTILE HEMANGIOMAS

CHI Formulary Development Project

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Abbreviations

AAP	American Academy of Pediatrics
BP	Blood Pressure
CADTH	Canadian Agency for Drugs and Technologies in Health
CHI	Council of Health Insurance
CPG	Clinical Practice Guideline
ECG	Electrocardiogram
EMA	European Medicines Agency
FDA	Food and Drug Administration
HAS	Haute Autorité de Santé
HR	Heart Rate
HTA	Health Technology Assessment
IDF	Insurance Drug Formulary
IH	Infantile Hemangioma
IIH	Intestinal Infantile Hemangioma
IQWIG	Institute for Quality and Efficiency in Health Care
MRA	Magnetic Resonance Angiography
MRI	Magnetic Resonance Imaging
mTOR	mammalian Target of Rapamycin
NICE	National Institute for Health and Care Excellence
PBAC	Pharmaceutical Benefits Advisory Committee
PHACE	Posterior fossa malformations – Hemangiomas – Arterial anomalies – Cardiac defects – Eye abnormalities–sternal cleft and supraumbilical raphe
RCT	Randomized Controlled Trial
SFDA	Saudi Food and Drug Authority

Executive Summary

Infantile hemangiomas (IHs) are benign vascular tumors frequently observed in infants and children. They manifest within the first weeks of life and undergo rapid growth during the first 6 to 12 months, followed by gradual reduction by the age of 5. Specific immunohistochemical markers, such as the erythrocyte-type glucose transporter protein, sets these vascular tumors apart from other benign vascular tumors[1].

The pathogenesis of IHs has yet to be fully defined. One prominent hypothesis suggests that circulating endothelial progenitor cells relocate to sites where conducive conditions like hypoxia and disturbances in developmental fields promote their growth.

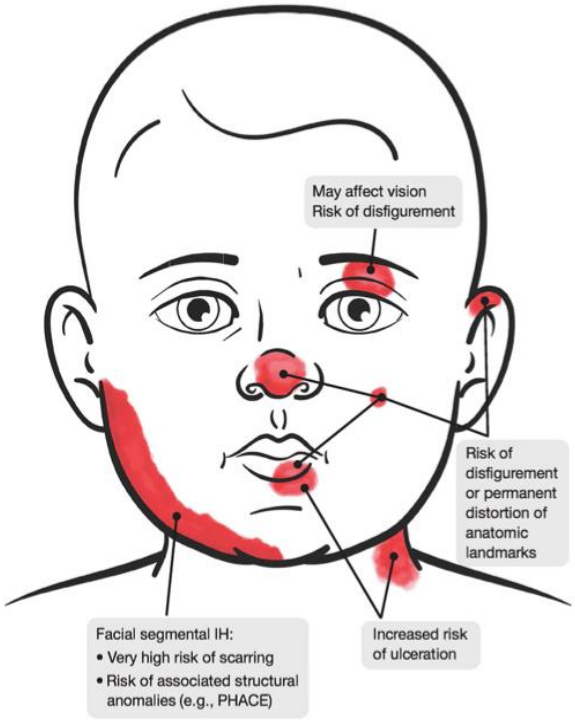


Figure 1. *High-risk infantile hemangiomas involving the face and the neck.*

Hemangiomas are categorized based on their depth within the soft tissue[2]:

- Superficial: they appear red and have little to no subcutaneous component (previously known as "strawberry" hemangiomas).
- Deep: these are blue in color and are situated beneath the skin's surface (previously referred to as "cavernous" hemangiomas).
- Combined (mixed): these have both superficial and deep components.

They can also be categorized according to their physical appearance:

- Localized: these are well-defined focal lesions that seem to originate from a central point.
- Segmental: these involve an anatomical region, often presenting as a plaque-like area and typically measuring over 5 cm in diameter.
- Indeterminate (undetermined): these do not clearly fit into the localized or segmental categories (often referred to as partial segmental).
- Multifocal: these consist of multiple distinct IHs located at different sites.

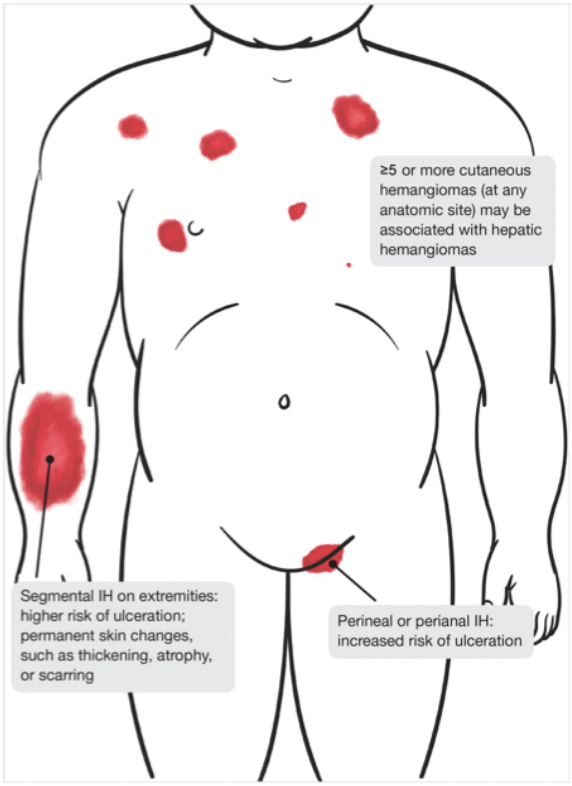


Figure 2. *High-risk infantile hemangiomas involving the truck/extremities/perineum.*

IHs occur in approximately 4% to 5% of infants, making them the most common benign vascular tumors of infancy. They are more common in girls, twins, infants born preterm or with low birth weight (up to 30% of infants born weighing < 1 kg are affected), and white neonates. Most rapid IH growth occurs between 1 and 3 months of age.

The prevalence of IHs in Middle Eastern countries, including Saudi Arabia, has not been extensively studied in terms of the epidemiological figures and clinical patterns. To address this gap, two studies, one prospective and the other retrospective, were conducted to assess the clinical features of IHs, associated risk

factors, and observe response patterns and adherence to oral propranolol among Saudi children undergoing treatment for infantile hemangioma[3,4].

Many infantile hemangiomas go through a natural process of growth and regression, with the majority not requiring any intervention. However, in 15% of cases, treatment is recommended when the hemangioma leads to functional challenges (such as obstructing vision, breathing, or feeding) or if it is in a critical area (such as near the eye, mouth, or airway), or if there are concerns about potential long-term cosmetic or functional effects. Ultimately, the decision to treat an infantile hemangioma is made on a case-by-case basis after careful evaluation by a healthcare professional. Without treatment, around one-third of hemangiomas cause some permanent skin change, and 10% are associated with long term changes that can impact on a child's development and socialization[5].

Since the first published report of infantile hemangioma responding to propranolol in 2008, propranolol has become the treatment of choice when systemic therapy is required due to its effectiveness in reducing the size and potentially preventing complications. Timolol, a beta-blocker like propranolol, is applied topically in the form of a gel or drops directly onto the hemangioma's surface. While not as potent as oral propranolol, it can be efficacious for smaller, superficial hemangiomas. Corticosteroids can be administered topically through creams or ointments, via direct injection (intralesional), or systemically through oral or intravenous means. Pulsed dye lasers are employed to target superficial hemangiomas and surgical excision might be contemplated in cases where the hemangioma poses significant functional or cosmetic concerns.

While first-line propranolol therapy is effective in the management of IHs, relapse rates have been reported to be as high as 30%[6]. A retrospective study published in the European Journal of Pediatrics in 2020 performed an analysis of all cases of IHs aged ≤ 12 months undergoing oral propranolol therapy in a 6-year period. Regrowth was observed in 18% of patients, with facial hemangiomas showing a high relapse rate as compared with other locations (25% versus 8.8%)[7].

This report compiles all clinical and economic evidence related to IHs according to the relevant sources. The ultimate objective of issuing IHs guidelines by the Council of Health Insurance (CHI) is to update the IDF (CHI Drug Formulary) with the best available clinical and economic evidence related to drug therapies, ensuring timely and safe access to IHs patients in Saudi Arabia. The focus of the review was on Saudi, American, European, and international guidelines issued within the last five years.

Several classes and drugs can be used for the management of IHs and are summarized in the table below.

Table 1. Summary of SFDA-Registered Drugs for the Management of Infantile Hemangiomas

Drug	Indication	Dose	Level of Evidence	HTA Recommendation
BETA ADRENERGIC RECEPTOR ANTAGONIST				
Propranolol hydrochloride	In IHs with life threatening complications, functional impairment and ulceration, structural anomalies (PHACE or LUMBAR syndrome), or with permanent disfigurement.	1 and 3 mg/kg twice daily, for 3 to 6 months. Can be decreased in preterm infants or those with faltering growth.	Level A; Strong recommendation.	Positive recommendation: IQWIG and CADTH.
Atenolol		1mg/kg/dose once daily for 6 months	Level B; Moderate recommendation.	No recommendations issued by the HTA bodies for Atenolol.
Timolol maleate 0.5% *(topical)*	For thin and/or superficial IHs. A concurrent use of propranolol and topical timolol can be prescribed.	One drop twice daily.	Level B; Moderate recommendation.	NICE considers its usage as off label in small and superficial IHs.
CORTICOSTEROIDS				
Prednisolone	A second line therapy in IHs if propranolol is contraindicated, poorly tolerated, or produces inadequate response.	2 and 5mg/kg per day for 4 to 12 weeks followed by a gradual taper by 9 to 12 months.	Level B; Moderate recommendation.	No recommendations issued by the HTA bodies for prednisolone.
Betamethasone *(intralesional injections)*	For focal, bulky, small, and localized His, in combination with Triamcinolone.	1.5 to 18mg/dose every 8 to 14 weeks.	Level B; Moderate recommendation.	No recommendations issued by the HTA bodies for Betamethasone.

Triamcinolone acetonide *(intralesional injections)*	For focal, bulky, small, and localized His, in combination with Betamethasone.	1 to 2mg/kg/dose every 4 to 6 weeks.	Level B; Moderate recommendation.	No recommendations issued by the HTA bodies for Triamcinolone acetonide.

It is important to emphasize that these treatment approaches serve as general recommendations. The appropriate treatment plan for each patient should be determined based on the specific type of IHs, as well as their overall health status. To provide a concise overview, the report will feature in section 3 a synthesis of key recommendations, focusing on the relevant drugs that align with these guidelines.

Section 1.0 Summary of Reviewed Clinical Guidelines and Evidence

1.1 KSA Guidelines

There are no specific guidelines for the treatment of IH in Saudi Arabia, consequently we will present the results of two studies, one prospective and the other retrospective.

1.1.1 A Retrospective Study of Infantile Hemangiomas: Demographic and Clinical Characteristics at Hera General Hospital, Makkah, Saudi Arabia (2018)

The objective of this study is to present the clinical features of IH and their associated risk factors. The study focused on patients diagnosed with IH, identified from the Dermatology Department's logbook at Hera General Hospital in Makkah, Saudi Arabia. Medical records of 61 patients were reviewed. Most patients received treatment with topical beta-blockers (39.7%), followed by pulsed-dye laser (10.3%) and systemic propranolol (10.3%)[4].

a. Systemic corticosteroid treatment

Systemic corticosteroids are a common treatment for hemangiomas, although their precise mechanism of action remains unclear. Typical daily doses of 2-3 mg of prednisolone or prednisone per kilogram of body weight were administered to the patients, while some researchers have suggested even higher doses (5 mg/kg daily). This treatment can lead to significant hemangioma shrinkage in approximately one-third of infants. In another third, it stabilizes growth without measurable shrinkage, and minimal or no response is observed in the remaining third, a pattern also seen in our cases. Despite potential side effects, such as irritability, gastrointestinal issues, immunosuppression, hypertension, and growth retardation, systemic steroid treatment remains a viable option in certain hemangioma cases, especially for patients unable to tolerate other treatments.

b. Propranolol therapy

Propranolol has become increasingly valuable in managing IH. Its efficacy for hemangioma treatment was serendipitously discovered by Leaute-Labreze et al. in 2008. A small portion of patients (10.3%) used this medication, leading to hemangioma stabilization. Propranolol's utility is supported by more than 170 reports and studies.

c. Topical agents

These are suitable for small, thin hemangiomas, offering fewer side effects than systemic agents, though their efficacy is not well-established. In this study, 23 patients (39.7%) used topical beta-blockers. Timolol maleate, a non-selective topical beta-blocker, was employed in the form of ophthalmic preparation. Reported adverse effects include severe sleep disturbance noted. In addition, administered orally or topically, timolol has been associated with various dysfunctions in the central nervous system, as documented in both individual case reports and larger patient series. Notably, these adverse events often resolve upon discontinuation of the drug. However, the existing studies on causation lack rigor and definitiveness, leading some to question the existence of a clear cause-and-effect relationship. Caution is recommended in its use, with experts advising no more than one drop twice a day on affected areas.

d. Laser therapy

Various laser systems have been used to treat hemangiomas. The flash lamp-pumped pulsed-dye laser, while effective for port-wine stains, is less efficient for hemangiomas. Only 10.3% of the patients received pulsed-dye laser treatment, resulting in only mild improvement. This laser's limited depth of penetration (around 1 mm) makes it better suited for thin, superficial hemangiomas rather than those with both superficial and deep components. However, it can be beneficial in improving residual telangiectasia after hemangioma involution and for treating ulcerated hemangiomas to reduce pain and promote rapid re-epithelialization.

1.1.2 The Response Pattern and Adherence to Oral Propranolol Among Saudi Children Treated for Infantile Hemangioma (2017)

Although oral propranolol's efficacy in treating IH is globally recognized, little is known about its effectiveness over time and patient adherence in Saudi Arabia. A prospective observational study was conducted between February 2012 and September 2015, involving children with problematic IH treated with oral propranolol at 2 mg/kg/day. Data on patient adherence (categorized by compliance with scheduled visits and treatment administration), lesion comparative response scores (relative improvement compared to previous visits), and potential side effects were collected during follow-up. Treatment was discontinued when significant improvement in the lesions was not observed. Serial digital photography was used for response and final outcome assessments.

The study's overall clinical outcomes of propranolol treatment for IH align with prior publications concerning safety and effectiveness. However, this research focuses on detailing patient adherence and response patterns to enhance our comprehension of patient interactions during propranolol treatment. Adherence by patients or

caregivers is a significant but often underestimated factor in evaluating treatment effectiveness. Non-adherence to prescribed medication or treatment plans is a leading cause of treatment failure, particularly in children with chronic illnesses.

Response patterns observed in the study indicate that the most significant improvement occurs within the initial two months of propranolol treatment, aligning with findings from prior studies. The conventional 6-month duration for propranolol treatment has been widely adopted but often based on historical practice rather than empirical evidence.

In this longitudinal study, the researchers documented an improvement pattern that peaks immediately after treatment initiation, sharply declines after four months, and continues at a reduced rate. No substantial improvements are observed beyond the 8-month mark. As a result, it is suggested that propranolol treatment should typically last for 6 months, with the possibility of extending it to 8 months in cases where noticeable effectiveness persists. Prolonging treatment beyond 8 months is unlikely to offer significant benefits, considering the natural involution tendency of infantile hemangiomas.

Nonetheless, patient adherence during the initial 8 months plays a pivotal role in treatment effectiveness and overall outcomes, emphasizing the importance of caregiver engagement, safety, and treatment effectiveness education. Sharing the expected response pattern with caregivers can be a valuable tool to improve compliance and enhance overall treatment satisfaction[3].

1.2 European Guidelines

1.2.1 Treatment of Infantile Hemangiomas: Recommendations of a European Expert Group (2015)

This paper provides an overview of current recommendations for managing complicated IH. The recommendations were formulated by a group of European experts through a consensus process, which involved a review of existing literature, multiple drafts, meetings with a quantitative voting system, and the creation of an approved final manuscript. While most hemangiomas are small and naturally regress without intervention, 5-10% of hemangiomas, often depending on their location, can lead to severe complications and require treatment. Propranolol has received approval from the FDA and EMA for treating IH, supported by a large confirmatory randomized controlled trial[8].

1.2.1.1 Diagnosis

- IHs are typically diagnosed through clinical evaluation.
- Large subcutaneous hemangiomas, especially those situated in the parotid, supraglottic, or paratracheal regions, may benefit from ultrasound with Doppler sonography, and some cases might require MRI. MRI is also advised for infants with multiple cutaneous IH to rule out hepatic hemangioma.
- Echocardiography is recommended for children with large hemangiomas due to their increased risk of developing high-output cardiac failure.
- Children with intrahepatic hemangiomas should undergo screening for hypothyroidism.
- Segmental hemangiomas of the face and neck are often associated with cerebrovascular and cardiac anomalies and should be screened using MRI angiography of the head and neck, along with echocardiography, ideally before starting propranolol therapy.

1.2.1.2 Management

The need for treatment of IH depends on specific indications. While IH often regress spontaneously by the second year of life, treatment is unnecessary in most cases. However, immediate therapy is required for all obstructive and ulcerated IH. Large hemangiomas may also necessitate treatment to prevent high-output cardiac failure. The introduction of oral propranolol therapy for IH has made many traditional treatment options obsolete, including topical, systemic, and surgical procedures that were used for many years.

a. Topical treatment

Among topical treatment options, the most promising one is the use of **topical beta blockers**. Case reports and case series have suggested the effectiveness of propranolol or timolol in topical applications.

- A randomized controlled trial (RCT) comparing timolol (15 patients) to a placebo (17 patients) has been published to date. Currently, there are no commercially available topical preparations specifically for treating IH. The existing topical beta blocker preparations lack standardization. Transcutaneous absorption of these topical agents, especially near the eye where transconjunctival absorption is a concern and in ulcerated areas, can lead to unexpected systemic effects. Hyperkalemia, an alarming and potentially life-threatening complication of β-blockers, has been rarely reported with topical timolol when used for infantile hemangiomas. Therefore, Timolol should be avoided in these cases[9].

- A randomized clinical trial that included patients with focal or segmental IH was conducted to evaluate the efficacy and safety of topical timolol for the treatment of IH in infants younger than 60 days. The patients were randomly assigned to receive either topical timolol or a placebo twice daily for 24 weeks. Changes in the size (volume, thickness) and color of the hemangiomas were evaluated at various time points. The results showed that topical timolol was well tolerated for the treatment of early proliferative IH. At week 4, the timolol group showed improvement in color compared to the placebo group. This suggests that topical timolol may have a positive effect on modifying the color of infantile hemangiomas. However, it provided limited benefit in terms of lesion resolution when given during the early proliferative stage[10].

Until more systematic studies establish their safety and efficacy, topical beta blockers cannot be recommended as a standard therapy for IH. However, they hold the potential to become the first-line treatment for small and superficial IH in problematic areas, potentially reducing the need for systemic treatment in a significant subset of children with IH.

b. Surgical treatment options

Surgical treatments were traditionally considered crucial for managing complicated IH for many years.

There is a lack of prospective studies that directly compare the effectiveness of laser surgery or cryosurgery with propranolol. However, retrospective studies suggest that oral propranolol is more effective than both surgical methods.

Cryosurgery may be considered in specific cases, but the supporting evidence for its use is mainly empirical. Cryosurgery may also disturb the skin colour. This may be seen as loss of normal colouration (hypopigmentation) or increased darkness (hyperpigmentation). Increased pigmentation typically fades after 3-4 months.

Conventional surgery is recommended for exceptionally rare cases where hemangiomas are resistant to propranolol therapy or in emergency situations. It also plays an important role in post-resolution reconstruction to remove excess skin and address remaining scarring.

c. Systemic treatment options

i. Propranolol

Two randomized controlled trials (RCTs) have been published, and various large case series and a meta-analysis of 1264 reported cases have shown that oral propranolol, administered at doses of 2-3 mg/kg/day for an average of 6 months, results in a response rate of 96-98%. Side effects are mostly reversible and benign. Sleep disturbance, somnolence, and irritability are observed in 15-25% of infants receiving

propranolol. The lipophilicity of beta blockers is linked to their ability to cross the blood-brain barrier, raising theoretical concerns about potential neurodevelopmental or cognitive side effects of propranolol.

Hypoglycemia and hypoglycemic seizures are significant risks associated with propranolol therapy. To prevent hypoglycemia, propranolol should be administered strictly during or after regular feedings.

Preliminary research suggests that hydrophilic beta blockers like nadolol and atenolol may prove to be as effective as propranolol for IH. Their hydrophilic nature suggests a reduced likelihood of central nervous system side effects. If confirmed through randomized controlled trials, these beta blockers, as well as others, might offer a viable alternative to propranolol for IH treatment. Additionally, the early use of topical beta blockers, such as propranolol or timolol, shows promise for superficial hemangiomas. Nevertheless, further studies are required to assess their effectiveness and safety.

Baseline measurements for HR and BP are essential. However, baseline glucose levels are only necessary for preterm or underweight infants, those with failure to thrive, or infants with a history of hypoglycemic episodes.

Hospital admission is recommended during the initiation of propranolol therapy, particularly for the most sensitive infant populations:

- All infants aged ≤ 2 months should be admitted for HR and BP monitoring at baseline, as well as after 1 and 2 hours.
- There is no consensus on whether these precautions should also apply to older infants (up to 3 months). Older infants might be admitted to a day clinic for baseline HR and BP checks, along with monitoring after dose increases.
- Infants weighing less than 3.5 kg, especially premature babies, should be admitted and monitored during dose escalation due to an increased risk of bradycardia and hypotension when treated with propranolol.
- Hospitalization is essential for all infants at immediate risk of life-threatening subglottic hemangioma.
- Children with significant comorbidities affecting the cardiovascular system, respiratory system, or blood glucose maintenance should also be admitted.
- Children with inadequate social support should be considered for hospital admission.

For inpatients, therapy should start at a dose of 1.0 mg/kg/day, with cardiovascular assessments conducted before and one and two hours after administering the prescribed dose. If well-tolerated, the propranolol dose can be increased to 2 mg/kg/day the following day if the child remains in the hospital.

Outpatients should have their dosage increased once weekly. If bradycardia or hypotension occurs, dose increases should be postponed or reduced.

The dosing interval is another consideration. In most studies, three equal doses were administered, but the multicenter study used two doses. Two doses given at least 9 hours apart are preferred for practical daily life.

The standard duration of therapy is six months, but in some children, treatment may be required for up to 12 months or longer. Six months of treatment is associated with a relapse rate of around 17-20%, while 12 months of treatment have a significantly lower relapse rate of 5%.

It is recommended to check the heart rate and adjust the dose based on increasing body weight every 4 weeks.

Therapy interruptions are necessary during episodes of obstructive bronchitis for as long as symptoms persist or when beta-mimetic inhalations are needed. Serious events, such as cardio-respiratory arrest following bronchiolitis in an infant receiving propranolol, have been documented.

ii. Corticosteroids

Retrospective studies comparing oral propranolol and corticosteroid treatment for IH have shown that propranolol therapy is more effective. It results in fewer surgical interventions and demonstrates better tolerance with minimal adverse effects. Two small RCT comparing propranolol and prednisolone therapy have been conducted, each involving 10 or fewer patients per study arm. In the first study, propranolol had a faster therapeutic effect than prednisolone, and a combination of both did not result in higher efficacy. In the other study, both medications were equally effective, with prednisolone showing a quicker response rate, while propranolol was significantly better tolerated.

Oral corticosteroids may still be considered for patients with complicated IH who do not respond to propranolol, exhibit primary contraindications, or experience side effects.

There's a proposed approach of using a combination of low-dose corticosteroids and propranolol for the treatment of segmental hemangiomas in patients with PHACES syndrome with cerebral vascular involvement. However, there's a theoretical concern that combining oral corticosteroids and propranolol may increase the risk of hypoglycemia, especially after discontinuing corticosteroids, due to the potential inhibition of counter-regulatory cortisol release.

iii. Sirolimus

Sirolimus, an inhibitor of the mammalian Target of Rapamycin (mTOR), has shown potent anti-angiogenic activity both in vitro and in kaposiform hemangioendothelioma. Case reports suggest it might be beneficial for complicated

IH as well. However, before any recommendations can be made regarding the role of sirolimus in IH, randomized controlled trials demonstrating its safety and efficacy are necessary.

1.2.2 British Society for Pediatric Dermatology Consensus Guidelines on Oral Propranolol in the Treatment of Proliferating Infantile Hemangiomas (2018)

In 2018, the British Society for Pediatric Dermatology released a consolidated set of clinical guidelines for the diagnosis and treatment of patients with IHs across the United Kingdoms and beyond. Recommendations are synthesized in the following section[5].

Indications for oral propranolol treatment

Most IHs do not necessitate treatment, as they typically resolve on their own without significant complications or long-lasting effects. Indications for treatment can be divided into three main categories:

- Ulceration is a common complication in IH, occurring in nearly 16% of children at the age of 4 months, typically during the rapid growth phase. The risk is significantly higher (around 50%) for IHs involving the lower lip and perineum. Ulcerations can be quite painful and often lead to scarring. If topical treatment proves ineffective or is not suitable, propranolol is the recommended treatment for ulcerated IH. However, for ulcerated IH beyond the growth phase, propranolol treatment is not necessary.
- Functional impairment:
    - Periocular IHs necessitate early intervention with propranolol if they are causing, or likely to cause, visual impairment. Failure to treat vision threatening IHs can result in severe and irreversible visual impairments, either by obstructing the visual axis, compressing the eye, or expanding into the retrobulbar space. Complications like amblyopia, significant refractive errors, and strabismus are observed in up to 80% of patients with untreated periocular IHs.
    - IHs on the lip may adversely affect feeding, particularly if they are ulcerated. Proper nursing care for ulceration is a crucial adjunct therapy.
    - Airway IHs can develop in infants without cutaneous lesions, although the risk is greater with segmental IHs located in a mandibular, cervicofacial, or 'beard' distribution. These cases require management in collaboration with an otorhinolaryngology specialist.

    - Treatment is warranted for IHs causing symptomatic obstruction of the ear canal, most seen in cases of recurrent infections.
- Risk of disfigurement: IH affecting the central face and ears have the potential to distort vital anatomical features, potentially leading to disfigurement. Even relatively small IHs on the nose, lips, and ears can result in long-lasting and socially stigmatizing alterations to the skin. Consequently, IHs located on the ears, nose, lips, forehead, cheeks, and thick IHs with a stepped border on the face should be considered for treatment with propranolol with a low threshold.

Absolute and relative contraindications to treatment with propranolol

Before initiating treatment for IH, the prescribing physician should conduct a screening for potential risks associated with oral propranolol. The contraindications for IH treatment with propranolol are listed below:

- Relative contraindications
    - Frequent wheezing
    - Blood pressure (BP) outside normal range for age
    - Heart rate (HR) outside normal range for age
- Absolute
    - Hypoglycemic episodes, recent or ongoing
    - Heart block, second and third degree
    - Hypersensitivity to propranolol

It is crucial to gather a comprehensive cardiovascular and respiratory history, paying particular attention to any history of wheezing, as well as inquiring about episodes of hypoglycemia and difficulties with feeding. In cases where the patient's heart rate and/or blood pressure fall outside the normal range for their age, treatment should be commenced in collaboration with a pediatrician or pediatric cardiologist.

Pretreatment investigations

The prescribing physician should perform a thorough assessment, including history, physical examination, and vital sign measurements. Routine electrocardiogram (ECG) and echocardiogram are not needed but may be considered in specific cases. No routine blood tests are required, but baseline glucose may be advisable in certain situations.

Propranolol hydrochloride oral solution 5mg/5ml

Treatment with propranolol can be initiated on an outpatient basis for infants over 4 weeks old, born full-term, with normal birthweight, established feeds, and appropriate weight gain, and without significant comorbidities. The starting dose is 1 mg/kg/day in three divided doses, which can be increased to 2 mg/kg/day after 24 hours.

For preterm infants or those with faltering growth, feeding difficulties and/or significant comorbidities such as hyperinsulinism, a typical starting dose is 0.5 mg/kg/day, but it's advisable to consult the local pediatrician or dermatologist for individualized dosing regimens. These infants should be admitted for 2-4 hours when initiating or increasing doses by more than 0.5 mg/kg/day. HR and BP should be monitored before the first dose and every 30 minutes for 2-4 hours after. Blood glucose checks are only necessary for those at risk of hypoglycemia. Parents should ensure regular feeding to minimize this risk. If feeding is reduced due to illness, propranolol should be temporarily stopped until normal feeding resumes.

The patient should be reviewed 2–3 months after starting treatment with propranolol. Patients with complicated IH might be reviewed sooner than that.

Cervicofacial segmental IH can sometimes be linked with PHACE (posterior fossa malformations–hemangiomas–arterial anomalies–cardiac defects–eye abnormalities–sternal cleft and supraumbilical raphe) syndrome, presenting a unique treatment challenge. While prompt intervention is often necessary for airway and periocular IH, using propranolol may heighten the hemodynamic risks associated with an otherwise asymptomatic cerebral arteriopathy. All patients with segmental IH in the head and neck area should undergo a cardiac evaluation, including ECG and echocardiogram interpreted by a pediatric cardiologist, prior to initiating propranolol. Ideally, a cerebral magnetic resonance angiogram (MRA) should also be conducted before starting propranolol treatment. In cases where an urgent MRA is not feasible, the initial propranolol dose should not exceed 0.5 mg/kg/day in three divided doses. If the MRA reveals arterial stenosis, it is essential to consult with a pediatric neurologist before initiating or increasing the dose of propranolol.

Propranolol should be temporarily discontinued if there is a notable decrease in oral intake or if the patient is experiencing wheezing that necessitates intervention. The treatment for IH should continue beyond the active growth phase to prevent a resurgence, and the decision on when to discontinue treatment should be based on clinical indicators. Terminating propranolol prematurely could result in renewed growth. While there isn't a universally agreed-upon age threshold for assessing the risk of regrowth, recent European research indicates that children aged 17 months or older face a considerably lower risk compared to younger age groups. Nevertheless,

for most patients, it is generally safe to conclude treatment between 12 to 14 months of age.

1.3 North American Guidelines

1.3.1 American Academy of Pediatrics (AAP) Clinical Practice Guideline for the Management of Infantile Hemangiomas (2019)

The American Academy of Pediatrics (AAP) has released its first clinical practice guideline (CPG) addressing the management of IHs. The goal of this CPG is to empower primary care providers with the knowledge and tools to confidently evaluate, prioritize, and manage IHs, all while adhering to evidence-based practices[11].

Risk stratification

While most IHs are small, benign, and resolve on their own without needing treatment, a notable minority may be considered as high risk and assessing them may demand a higher level of experience and expertise (Level X, strong recommendation). The high-risk IHs, along with their associated clinical indications, are outlined in Table 2 below:

Table 2. High-Risk Infantile Hemangiomas

IH Clinical Findings	IH Risk
LIFE-THREATENING	
"Beard-area" IH	Obstructive airway hemangiomas.
≥ 5 cutaneous IHs	Liver hemangiomas, cardiac failure, hypothyroidism.
FUNCTIONAL IMPAIRMENT	
Periocular IH (>1 cm)	Astigmatism, anisometropia, proptosis, amblyopia.
IH involving lip or oral cavity	Feeding impairment.
ULCERATION	
Segmental IH: IH of any size involving any of the following sites: lips, columella, superior helix of ear, gluteal cleft and/or perineum, perianal skin, and other intertriginous areas (e.g., neck, axillae, inguinal region)	Increased risk of ulceration.
ASSOCIATED STRUCTURAL ANOMALIES	

Segmental IH of face or scalp	PHACE syndrome indicates posterior fossa IH, cardiovascular anomalies, cerebrovascular anomalies, and eye anomalies.
Segmental IH of lumbosacral and/or perineal area	LUMBAR syndrome indicates lower body IH and other cutaneous defects like urogenital IH.
DISFIGUREMENT	
Segmental IH, especially of face and scalp	High risk of scarring and/or permanent disfigurement.
Facial IH (measurements refer to size during infancy): nasal tip or lip (any size) or any facial location ≥2 cm (>1 cm if ≤ 3 months of age)	Risk of disfigurement via distortion of anatomic landmarks and/or scarring and/or permanent skin changes.
Scalp IH > 2 cm	Permanent alopecia (especially if the hemangioma becomes thick or bulky); profuse bleeding if ulceration develops (typically more bleeding than at other anatomic sites).
Neck, trunk, or extremity IH >2 cm, especially in growth phase or if abrupt transition from normal to affected skin (i.e., ledge effect); thick superficial IH (e.g., ≥2 mm thickness)	Greater risk of leaving permanent scarring and/or permanent skin changes depending on anatomic location.
Breast IH (female infants)	Permanent changes in breast development (eg, breast asymmetry) or nipple contour.

Imaging

- Do not perform imaging unless the diagnosing of IH is uncertain, ≥5 cutaneous IHs are present, or suspicions of associated anatomical abnormalities arise (Level B, moderate recommendation).
- An abdominal ultrasonography is considered as the primary imaging method when the diagnosis of IH is uncertain, especially for screening hepatic IH (Level C, weak recommendation).
- A magnetic resonance imaging (MRI) and/or magnetic resonance angiography (MRA) may be considered in cases where there are concerns

about potential associated structural abnormalities, such as PHACE syndrome or LUMBAR syndrome (Level B, moderate recommendation).

Pharmacotherapy

a. Propranolol hydrochloride

- Oral propranolol, a nonselective antagonist of both beta 1 and beta 2 adrenergic receptors, is considered as the first-line agent for IHs requiring systemic treatment (Level A; strong recommendation).
- Although the precise mechanisms by which propranolol affects IHs are not fully understood, it is conjectured to involve vasoconstriction, inhibition of angiogenesis, initiation of apoptosis, suppression of nitric oxide production, and modulation of the renin-angiotensin system.
- The recommended dosage ranges between 1 and 3 mg/kg twice daily for 3 to 6 months unless there are comorbidities (e.g., PHACE syndrome) or adverse effects (e.g., sleep disturbance) that necessitate a lower dose (Level A; moderate recommendation). Some
- It is advised to administer propranolol with or after feeding and that doses be held at times of diminished oral intake or vomiting to reduce the risk of hypoglycemia, as propranolol can affect glycogenolysis and gluconeogenesis (Level X; strong recommendation).
- Patients should be assessed for potential adverse effects of propranolol, and caregivers should be educated about these, including sleep disturbances, bronchial irritation, and clinically symptomatic bradycardia and hypotension (Level X; strongly recommended). These symptoms tend to be mild and asymptomatic.
- In a meta-analysis of 18 studies, propranolol consistently demonstrated greater effectiveness and displayed a superior safety profile when compared to alternative treatment options like systemic or intralesional corticosteroids, pulsed-dye laser therapy, or placebo.
- There is limited available data regarding the efficacy of β-blockers other than propranolol or alternative methods of administering propranolol.

b. Corticosteroids

For several decades, systemic therapy with corticosteroids was the established standard of care until it was replaced by oral propranolol. Presently, prednisone is employed to address IHs in cases where there are contraindications to oral propranolol or where the treatment is ineffective or poorly tolerated (Level B; moderate recommendation).

Typical protocols include treatment with a dose range between 2 and 5 mg/kg per day for 4 to 12 weeks followed by a gradual taper by 9 to 12 months.

In cases of focal, bulky, small, and localized IHs, intralesional injections of triamcinolone and/or betamethasone every 4 to 6 weeks may be recommended (Level B; moderate recommendation).

c. Topical timolol maleate

Topical timolol maleate, a nonselective beta-adrenergic receptor antagonist, may be prescribed as a therapy for thin and/or superficial IHs (Level B; moderate recommendation).

d. Surgical management

While surgery and pulsed-dye laser therapy may be considered as treatment options for specific cases of IHs (Level C; moderate recommendation), their use has become less common with the introduction of β-blocker therapy. Generally, surgical interventions are discouraged during infancy due to increased risks associated with anesthesia, the tumor's highly vascular nature, which heightens the potential for blood loss and iatrogenic injury, and the potential for a less favorable outcome.

e. Parent education

Healthcare providers should take the opportunity to inform parents of infants affected by an IH about the condition in details including the expected natural history and the potential risks it poses for complications or potential disfigurement (Level X; strong recommendation).

1.4 International Guidelines

1.4.1 Australasian College of Dermatologists Consensus Statement for the Treatment of Infantile Hemangiomas with Oral Propranolol (2017)

The Australasian Vascular Anomalies Network and the Australasian Paediatric Dermatology Network of the Australasian College of Dermatologists have developed a consensus statement for the treatment of infantile hemangiomas with oral propranolol[12].

Indication for treatment

1. Life-threatening or functionally impairing infantile hemangiomas can manifest in various ways:
    - Airway Hemangioma

    - Visual Impairment (posing a risk of amblyopia due to visual obstruction or pressure-induced astigmatism)
    - Spinal Cord Involvement
    - High-flow Hemangioma with Cardiac Compromise (e.g., large hepatic lesions)
    - Hemangiomas Leading to Hypothyroidism
    - Large Hemangiomas Interfering with Physical Development
2. Ulcerated hemangiomas causing significant pain are also a concern: if standard wound care proves ineffective, the consideration of propranolol, laser treatment, or early surgery in conjunction with propranolol may be warranted.
3. Hemangiomas at notable risk of ulceration are typically found on the lips and perineum.
4. Hemangiomas with a significant risk of causing deformity and/or psychosocial impact can have different implications over time:
    - In the short term, many untreated hemangiomas may still be noticeable between 3 to 8 years of age. Adverse psychosocial effects may start to manifest before this age, underscoring the consideration for early treatment.
    - In the long term, hemangiomas can result in lasting alterations, including deformity, scarring, atrophy, telangiectasia, and excess skin. High-risk areas, such as the lips, nose, cheeks, and ears, pose challenges for surgical repair. Untreated nasal tip lesions often lead to permanent nasal cartilage deformity. Hemangiomas with a step-edge or cobblestone surface frequently result in enduring changes.

Imaging

- For hemangiomas in a beard distribution, be mindful of potential airway involvement. Consider using indirect laryngoscopy.
- Segmental head and neck infantile hemangiomas signal an elevated risk of PHACE syndrome. Contemplate an echocardiogram, as well as MRI and magnetic resonance angiography of the head and neck. Ophthalmology assessment is also recommended.
- In cases of segmental lumbar and pelvic hemangiomas, there may be associations with anogenital, renal, or spinal anomalies. Consider performing ultrasound or MRI of the spine, along with a renal ultrasound.
- Infants with more than four infantile hemangiomas warrant consideration for hepatic ultrasound, as well as ultrasound or MRI of the head.

- Be aware that large infantile hemangiomas can be linked to hypothyroidism and high output cardiac failure.

Early treatment options

a. Oral propranolol:

Oral propranolol is the initial treatment of choice for infantile hemangiomas that require intervention.

Conditions like hypoglycemia, bradycardia, bronchospasm, and intracranial arterial anomalies are relative contraindications for propranolol. Seeking specialist advice is recommended in these situations.

For healthy infants, the introduction of oral propranolol can typically be done on an outpatient basis, with the initial dose administered at home. Begin with a dose of 1–2 mg/kg per day, divided into two doses taken 8–12 hours apart. After 1–2 weeks, increase to 2 mg/kg per day, unless a lower dose proves effective. If the response is inadequate, consider increasing the dosage of propranolol to 3 mg/kg per day.

In smaller infants (0–4 weeks corrected age or small for gestational age, or less than 2.5 kg body weight) and those with other clinical concerns (e.g., at risk for hypoglycemia), consider:

- Initiating therapy during an inpatient stay or as a day procedure.
- Starting with a lower initial dose (e.g., 0.5 mg/kg per day).
- Dividing the daily dose into three rather than two doses.
- Adopting a more gradual dosage escalation.

For these higher-risk infants, contemplate hourly heart rate monitoring for 3 hours and checking glucose levels 3 hours after the initial dose and any subsequent dose increases. All parents should be provided with written instructions to discontinue propranolol if their child is unwell or experiencing feeding difficulties.

The optimal treatment duration with propranolol varies from 3 to 24 months. Propranolol can be stopped safely without the need for weaning the dosage.

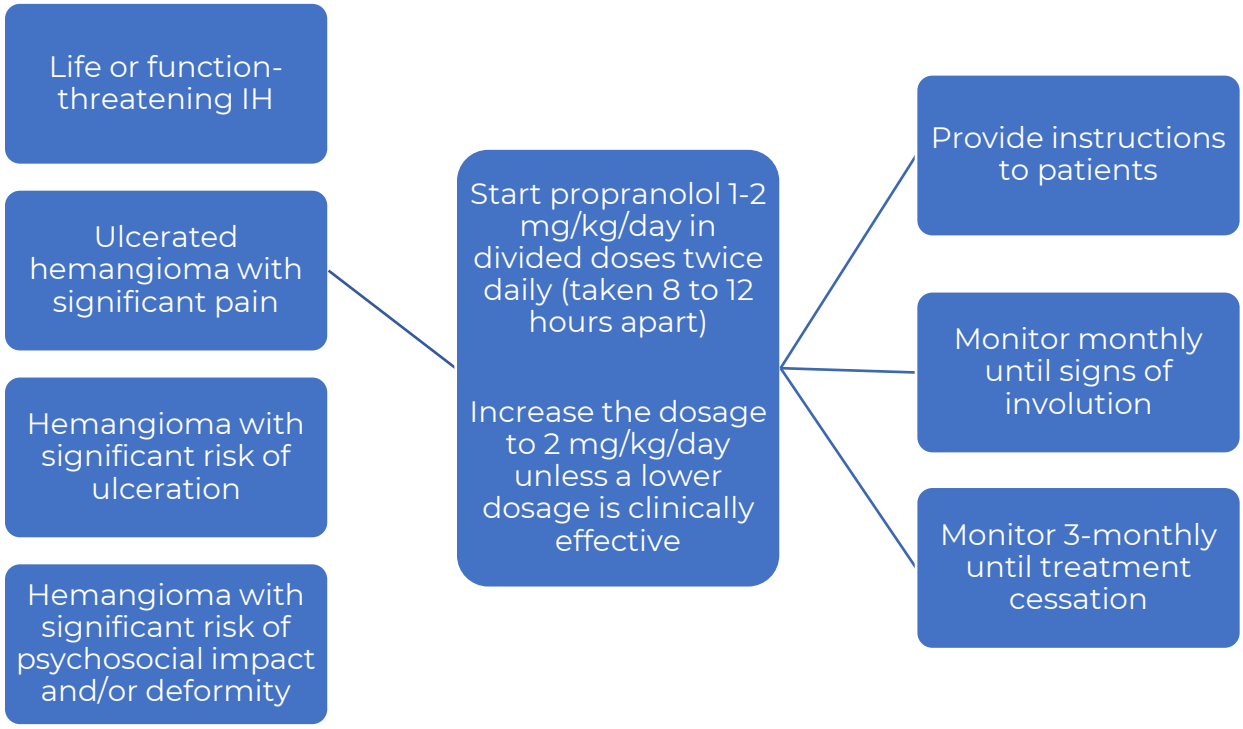


Figure 3. *Guidelines of propranolol treatment for infantile hemangiomas.*

b. Topical beta-blocker:

The application of a topical beta-blocker can be beneficial for certain superficial hemangiomas but is generally less effective than the oral form. The most utilized topical beta-blocker is timolol maleate 0.5% in gel form, administered as one drop onto the lesion twice daily. While the systemic absorption of topical timolol is typically limited, it may be more significant in cases of ulcerated lesions, large lesions, or in infantile hemangiomas affecting premature or small infants.

c. Systemic steroids:

In the past, high-dose systemic steroids at a dosage of 2 mg/kg per day were frequently employed. However, they are no longer the primary treatment option. They may be contemplated for patients for whom oral beta-blockers are not advisable or have proven ineffective.

d. Surgery:

Surgery is generally unnecessary for most IH. It can be a viable treatment option, either on its own or in combination with oral propranolol, for localized ulcerated lesions. Additionally, in cases where significant psychosocial effects may be reduced through early surgical intervention, it can be considered.

e. Pulsed-dye laser:

Lasers, particularly pulsed dye lasers, are used to target superficial hemangiomas. The laser emits light energy that is absorbed by the hemangioma's blood vessels, causing them to close off. This treatment is effective for reducing the redness and thickness of the hemangioma. Laser treatment may also be beneficial for ulcerated lesions that do not respond to appropriate dressings.

1.5 Systematic Reviews/Meta-Analyses

Table 3. Systematic Reviews and Meta-Analyses

Author (Year)	Title	Objective	Primary Outcome	Results
Kleinman et al. (2023)[13]	Sirolimus for diffuse intestinal infantile hemangioma with PHACE features: systematic review	3-month-old female with cardiovascular anomalies and diffuse intestinal infantile hemangioma (IIH) of the small bowel suggesting possible diagnosis of PHACE syndrome. The GI symptoms persisted under treatment with propranolol, whereas the addition of sirolimus led to regression of the IIH.	N/A	A total of 4933 articles were identified; 24 articles met inclusion criteria with 46 IIH cases. The most common GI presentations were unspecified GI bleed (40%) and anemia (38%). The most common treatments were corticosteroids (63%), surgical resection (32.6%), and propranolol (28%). Available outcomes were primarily bleeding arrest (84%). Nine cases (19.5%) were diagnosed with definite PHACE, 5 (11%) with possible PHACE, and 32 (69.5%) no PHACE. The reported case presented with symptoms most consistent with those of possible PHACE and definite PHACE. No cases in this review underwent treatment with sirolimus. **This is the first reported case of successful treatment of IIH with sirolimus.**

Chen et al. (2023)[14]	Should Propranolol Remain the Gold Standard for Treatment of Infantile Hemangioma? A Systematic Review and Meta-Analysis of Propranolol Versus Atenolol	Although propranolol has been established as the gold standard when treatment is sought for infantile hemangioma, concerns over its side effect profile have led to increasing usage of atenolol, a beta-1 selective blocker.	Complete response rate; Hemangioma Activity Score; adverse events	A total of 669 participants in 7 studies (3 RCTs and 4 cohort) were included. Propranolol showed a significantly higher rate of complete response compared to atenolol (73.3% vs 85.4%, *P* = .0004). The pooled mean difference of 0.07 (95% CI -0.12, 0.27) in Hemangioma Activity Score was not statistically significant. In terms of side effects, there were significantly more agitation and bronchial hyperreactivity events in the propranolol group (*P* = .0245 and *P* < .0001, respectively). Overall, there was a significantly greater number of adverse events in the propranolol group compared to the atenolol group (185 vs 117, *P* < .00001). **Propranolol treatment leads to a significantly higher rate of complete response than atenolol. However, its use must be weighed against its greater side effect profile.**
Huang et al. (2022)[15]	Comparison of the efficacy and safety	Investigate the efficacy and safety	Response rate	Ten RCTs with a total of 979 patients with IH were included in

	of lasers, topical timolol, and combination therapy for the treatment of infantile hemangioma: A meta-analysis of 10 studies	of topical timolol alone or lasers plus topical timolol versus lasers alone for the treatment of IH.		this meta-analysis. Treatment with topical timolol alone was as effective as lasers in treating IH (risk ratio [RR] = 0.99, p = 0.94), with similar adverse events. The difference was not statistically significant (RR = 1.67, p = 0.14). Combined treatment with topical timolol and lasers showed a favorable response rate compared with treatment with either lasers (RR = 1.23, p = 0.01) or topical timolol (RR = 1.35, p = 0.001) alone. Furthermore, compared to topical timolol alone, the combined treatment indicated similar risks of adverse events (RR = 0.70, p = 0.38) but fewer risks of adverse events (RR = 0.39, p = 0.004) compared to lasers alone. This meta-analysis provided evidence that a combined treatment with topical timolol and lasers might be more effective than a single treatment strategy in infants with IH, and with no significant increase in adverse reactions.

Section 2.0 Drug Therapy

2.1 Corticosteroids

2.1.1 Prednisolone

Information on Prednisolone is detailed in the table below[16].

Table 4. Prednisolone Drug Information

SCIENTIFIC NAME PREDNISOLONE	
SFDA Classification	Prescription
SFDA	Yes
US FDA	Yes
EMA	Yes
MHRA	Yes
PMDA	Yes
Indication (ICD-10)	D18.0
Drug Class	CORTICOSTEROIDS FOR SYSTEMIC USE, PLAIN
Drug Sub-class	GLUCOCORTICOIDS
ATC Code	H02AB04
Pharmacological Class (ASHP)	Glucocorticoids
DRUG INFORMATION	
Dosage Form	Oral solution
Route of Administration	Oral use
Dose (Adult) [DDD]*	N/A
Maximum Daily Dose Adults*	N/A
Dose (pediatrics)	2 to 3 mg/kg/day up to 5 mg/kg/day; may be administered once daily or in divided doses up to 4 times daily; duration depends on response rate, patient age, and phase of hemangioma growth, but usually ranges for 4 to 12 weeks followed by a gradual taper and completion of therapy by 9 to 12 months of age.
Maximum Daily Dose Pediatrics*	N/A

Adjustment	N/A
Prescribing edits*	**ST**
AGE (Age Edit):	N/A
CU (Concurrent Use Edit):	N/A
G (Gender Edit):	N/A
MD (Physician Specialty Edit):	N/A
PA (Prior Authorization):	N/A
QL (Quantity Limit):	N/A
ST (Step Therapy):	Prednisolone is used if oral propranolol is contraindicated, poorly tolerated, or produces inadequate response.
EU (Emergency Use Only):	N/A
PE (Protocol Edit):	N/A
SAFETY	
Main Adverse Drug Reactions (Most common and most serious)	Adrenal suppression (tertiary adrenal insufficiency), cardiovascular effects (hypertension and dyslipidemia), CNS and psychiatric/behavioral effects, Cushingoid features/Cushing syndrome, hyperglycemia, infection, neuromuscular and skeletal effects (osteoporosis), ocular effect (glaucoma).
Drug Interactions	**Category X:** • Aldesleukin • Brivudine • Brivudine • Cladribine • Desmopressin • Disulfiram • Mifamurtide • Natalizumab • Pimecrolimus • Ruxolitinib • Tacrolimus • Tertomotide • Vaccines like Mumps- Rubella- or Varicella-Containing Live Vaccines
Special Population	Pediatric, older patients.

Contraindications	Hypersensitivity to prednisolone, administration of live or live attenuated vaccines with immunosuppressive doses of prednisone; systemic fungal infections.
Monitoring Requirements	• Blood pressure • Serum glucose • Growth in pediatric • Bone mineral density
Precautions	Hepatic and renal impairments, Myasthenia gravis, perforation risk in patients with GI diseases.
Black Box Warning	N/A
REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

A search for clinical economic recommendations from the HTA bodies, including the National Institute for Health and Care Excellence (NICE), the Canadian Agency for Drugs and Technologies in Health (CADTH), the Haute Autorité de Santé (HAS), the Institute for Quality and Efficiency in Health Care (IQWIG), and the Pharmaceutical Benefits Advisory Committee (PBAC), didn't yield any guidance for prednisolone in infantile hemangiomas. This is probably because treatment paradigms haven't much changed in the last decade, with no new drugs introduced in the management landscape. Prednisolone has been marketed worldwide for decades and various generics are available, leading to a relatively low cost of treatment.

CONCLUSION STATEMENT – Prednisolone

Prednisolone is a synthetic glucocorticoid derived from cortisone, used to treat various diseases with anti-inflammatory or immunosuppressive effects. It is sometimes utilized in the treatment of IHs, particularly in cases where other interventions like propranolol may not be suitable or effective. Typically, oral prednisolone may be prescribed at a dosage of 2-3 mg/kg per day, divided into two or three doses. However, it's crucial to note that the use of prednisolone should be carefully monitored by a healthcare professional, as corticosteroids can have potential side effects, particularly when used over an extended period or at high doses. There are no recommendations issued by the HTA bodies for prednisolone.

2.1.2 Betamethasone

Information on Betamethasone is detailed in the table below[17].

Table 5. Betamethasone Drug Information

SCIENTIFIC NAME BETAMETHASONE	
SFDA Classification	Prescription
SFDA	Yes
US FDA	N/A
EMA	N/A
MHRA	N/A
PMDA	N/A
Indication (ICD-10)	D18.0
Drug Class	Corticosteroid
Drug Sub-class	Glucocorticoid
ATC Code	D07XC01
Pharmacological Class (ASHP)	Adrenals
DRUG INFORMATION	
Dosage Form	Suspension for injection
Route of Administration	Intralesional
Dose (pediatrics)	**IH, severe: Limited data available: Infants and Children: Intralesional:** Dosage dependent upon size of lesion: Commonly reported: 6 mg administered as a 6 mg/mL (in combination with triamcinolone injection) divided into multiple injections along the lesion perimeter; reported range: 1.5 to 18 mg/dose; doses usually administered every 8 to 14 weeks; reported range: 6 to 25 weeks.
Maximum Daily Dose Pediatrics	N/A
Adjustment	There are no dosage adjustments
Prescribing edits	**CU**
AGE (Age Edit):	N/A
CU (Concurrent Use Edit):	May be used in combination with intralesional triamcinolone acetonide.

G (Gender Edit):	N/A
MD (Physician Specialty Edit):	N/A
PA (Prior Authorization):	N/A
QL (Quantity Limit):	N/A
ST (Step Therapy):	N/A
EU (Emergency Use Only):	N/A
PE (Protocol Edit):	N/A
SAFETY	
Main Adverse Drug Reactions (Most common and most serious)	-Dermatologic: Erythema, exfoliation of skin, fragile skin, hair, urticaria, xeroderma -Endocrine & metabolic: Growth suppression -Local: Injection site reaction, post injection flare
Drug Interactions	Category X: • BCG Products • Brivudine • Desmopressin
Special Population	Pediatric: May affect growth velocity; growth should be routinely monitored in pediatric patients.
Contraindications	-Hypersensitivity to any component of the formulation. -Use in areas with local infection.
Monitoring Requirements	Intraocular pressure (if therapy >6 weeks); weight, height, and linear growth (with chronic use); assess HPA suppression. Monitor blood pressure, serum glucose, potassium, calcium, hemoglobin, occult blood loss, and clinical presence of adverse effects.
Precautions	-Adrenal suppression with failure to thrive has been reported in infants after receiving intralesional corticosteroid injections for treatment of hemangioma. -May cause inhibition of bone growth in pediatric patients.

Black Box Warning	N/A
REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

A search for clinical economic recommendations from various HTA bodies including NICE, CADTH, HAS, IQWIG, and PBAC, didn't yield any guidance for on the use of betamethasone in IH.

CONCLUSION STATEMENT-Betamethasone

Betamethasone is indicated in cases of focal, bulky, small, and localized IHs. Intralesional injections of betamethasone every 4 to 6 weeks may be recommended. Betamethasone may affect growth velocity; growth should be routinely monitored in pediatric patients.

2.1.3 Triamcinolone Acetonide

Information on Triamcinolone acetonide is detailed in the table below.

Table 6. Triamcinolone Acetonide Drug Information.

SCIENTIFIC NAME TRIAMCINOLONE ACETONIDE	
SFDA Classification	Prescription
SFDA	Yes
US FDA	N/A
EMA	N/A
MHRA	N/A
PMDA	N/A
Indication (ICD-10)	D18.0
Drug Class	Corticosteroid
Drug Sub-class	Glucocorticoid
ATC Code	H02AB08
Pharmacological Class (ASHP)	Adrenals
DRUG INFORMATION	
Dosage Form	Suspension for injection
Route of Administration	Intralesional
Dose (pediatrics)	**IH, severe: Limited data available: Infants and Children: Intralesional:** Dosage dependent upon size of lesion:

	Commonly reported: 1 to 2 mg/kg/dose administered in divided doses along the lesion perimeter ~monthly (4 to 5 weeks most frequently reported interval), has also been used in combination with betamethasone intralesional injections.
Maximum Daily Dose Pediatrics	30 mg/dose
Adjustment	There are no dosage adjustments
Prescribing edits	**CU**
AGE (Age Edit):	N/A
CU (Concurrent Use Edit):	May be used in combination with intralesional betamethasone.
G (Gender Edit):	N/A
MD (Physician Specialty Edit):	N/A
PA (Prior Authorization):	N/A
QL (Quantity Limit):	N/A
ST (Step Therapy):	N/A
EU (Emergency Use Only):	N/A
PE (Protocol Edit):	N/A
SAFETY	
Main Adverse Drug Reactions (Most common and most serious)	-Hematologic and oncologic: bruise Neuromuscular: joint swelling -Endocrine & metabolic: Growth suppression -Local: Injection site reaction, post injection flare
Drug Interactions	Category X: • BCG Products • Brivudine • Desmopressin • Aldesleukin • Cladribine • Macimorelin • Mifamurtide • Natalizumab • Ritlecitinib • Tacrolimus • Pimecrolimus

Special Population	Pediatric: May affect growth velocity; growth should be routinely monitored in pediatric patients.
Contraindications	-Hypersensitivity to any component of the formulation. -Use in areas with local infection.
Monitoring Requirements	Intraocular pressure (if therapy >6 weeks); weight, height, and linear growth (with chronic use); assess HPA suppression. Monitor blood pressure, serum glucose, potassium, calcium, hemoglobin, occult blood loss, and clinical presence of adverse effects.
Precautions	-Adrenal suppression with failure to thrive has been reported in infants after receiving intralesional corticosteroid injections for treatment of hemangioma. -May cause inhibition of bone growth in pediatric patients. -Anaphylactic reactions. -Immunosuppression.
Black Box Warning	N/A
REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

A search for clinical economic recommendations from the HTA bodies, including the National Institute for Health and Care Excellence (NICE), the Canadian Agency for Drugs and Technologies in Health (CADTH), the Haute Autorité de Santé (HAS), the Institute for Quality and Efficiency in Health Care (IQWIG), and the Pharmaceutical Benefits Advisory Committee (PBAC), didn't yield any guidance for triamcinolone acetonide in infantile hemangiomas. This is probably because treatment paradigms haven't much changed in the last decade, with no new drugs introduced in the management landscape.

CONCLUSION STATEMENT – Triamcinolone acetonide

Triamcinolone is a corticosteroid with anti-inflammatory and immunosuppressive properties, primarily acting by inhibiting the synthesis of various inflammatory mediators. In the context of IH, triamcinolone acetonide can

be injected directly into the lesion to reduce its size and improve cosmetic outcomes. The usual dose depends on the size and location of the hemangioma but typically ranges from 1 to 3 mg/kg, every 4 to 6 weeks . Triamcinolone is sometimes combined with betamethasone, another corticosteroid, to enhance its therapeutic effects. The combination may provide a more comprehensive anti-inflammatory response. However, it's crucial to note that the use of corticosteroids in infantile hemangioma requires careful consideration of potential side effects, including skin atrophy, telangiectasia, and hypothalamic-pituitary-adrenal axis suppression. Close monitoring and appropriate dosage adjustments are essential to mitigate these risks and ensure the safety of the pediatric patient.

2.2 Beta Blockers

2.2.1 Timolol Maleate 0.5%

Information on Timolol maleate 0.5% is detailed in the table below[18].

Table 7. Timolol Maleate Drug Information

SCIENTIFIC NAME TIMOLOL MALEATE 0.5%	
SFDA Classification	Prescription
SFDA	Yes
US FDA	Yes
EMA	Yes
MHRA	Yes
PMDA	Yes
Indication (ICD-10)	D18.0
Drug Class	NON-SELECTIVE BETA BLOCKING AGENTS
Drug Sub-class	NON-SELECTIVE BETA BLOCKING AGENTS
ATC Code	S01ED01
Pharmacological Class (ASHP)	Beta blocking agents
DRUG INFORMATION	
Dosage Form	Gel forming solution
Route of Administration	Topical use
Dose (Adult) [DDD]*	N/A
Maximum Daily Dose Adults*	N/A
Dose (pediatrics)	1 drops twice daily to the site.

Maximum Daily Dose Pediatrics*	N/A
Adjustment	N/A
Prescribing edits*	**CU**
AGE (Age Edit):	N/A
CU (Concurrent Use Edit):	A concurrent use of topical timolol and oral propranolol can be prescribed.
G (Gender Edit):	N/A
MD (Physician Specialty Edit):	N/A
PA (Prior Authorization):	N/A
QL (Quantity Limit):	N/A
ST (Step Therapy):	N/A
EU (Emergency Use Only):	N/A
PE (Protocol Edit):	N/A
SAFETY	
Main Adverse Drug Reactions (Most common and most serious)	Local irritation, blurred vision, hypersensitivity reactions, hypotension and bronchospasm may occur due to systemic absorption of timolol.
Drug Interactions	**Category X:** • Etofillyne • Fexinidazole • Rivastigmine
Special Population	Contact lenses wearers
Contraindications	Chronic obstructive pulmonary disease, bronchial asthma, hypersensitivity to timolol.
Monitoring Requirements	• Blood pressure • Intraocular pressure
Precautions	Hypersensitivity and anaphylactic reactions.
Black Box Warning	N/A
REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of IHs treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health

Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable. The recommendations below are for timolol maleate.

Table 8. Timolol Maleate HTA Recommendations

MEDICATION	AGENCY	HTA RECOMMENDATION
Timolol maleate 0.5%	NICE[19]	14 August 2015 The use of topical timolol is considered off-label for the treatment of infantile hemangiomas. The evidence suggests that it may reduce the redness of superficial hemangiomas and potentially decrease their size or volume. However, the clinical significance of these changes is not entirely clear. Adverse events related to systemic absorption of timolol are rare, but potential side effects include bradycardia, hypotension, bronchospasm, and sleep disturbances. It's important to note that neither topical timolol nor most oral propranolol preparations are licensed for treating infantile hemangiomas. Topical timolol may be considered for small, superficial hemangiomas, particularly if they are in areas where resolution may be incomplete, ulcerating, or interfering with essential functions or development. It is important to note that neither topical timolol nor most oral propranolol preparations are licensed specifically for treating infantile hemangiomas. **No cost-effectiveness studies were identified that assessed the use of off-label topical timolol for treating infantile hemangioma.**
	CADTH, IQWIG, PBAC, HAS	N/A

CONCLUSION STATEMENT – Timolol maleate 0.5%

Topical timolol, a nonselective β-adrenergic drug, has gained attention for treating superficial IHs, with a recent meta-analysis suggesting its effectiveness and safety, albeit with low to moderate quality evidence. Furthermore, a pilot randomized clinical trial specifically focused on assessing the efficacy and safety of timolol maleate solution, 0.5%, during the first 60 days of life. Despite the twice-daily application for 24 weeks, the study did not find topical timolol to be effective for early proliferative IH treatment, except for an early improvement in lesion color at week 4. This early improvement may be highly desired for some families for whom visible IHs may cause social stigma. Those studies suggest the need for larger multicenter trials to establish the efficacy of this treatment further. Adverse effects from systemic absorption of timolol are possible, although they are generally rare when used topically for treating infantile hemangiomas. These may include bradycardia (slow heart rate), hypotension (low blood pressure), bronchospasm (constriction of the airways), peripheral vasoconstriction, weakness and fatigue, sleep disturbance, and hypoglycemia (low blood sugar levels). When considering the concomitant use of topical timolol and oral propranolol, it's important to consult a healthcare professional for personalized advice and treatment options. According to the NICE, topical timolol maleate has shown effectiveness in reducing the redness and size of superficial His, but the clinical significance of these changes remains somewhat uncertain. There is limited high-quality evidence available, mainly from small studies.

2.2.2 Propranolol

Information on Propranolol is detailed in the table below[20].

Table 9. Propranolol Drug Information

SCIENTIFIC NAME PROPRANOLOL	
SFDA Classification	Prescription
SFDA	Yes
US FDA	Yes, March 2014
EMA	Yes
MHRA	Yes
PMDA	Yes
Indication (ICD-10)	D18.0
Drug Class	Beta-Adrenergic Blockers
Drug Sub-class	Non-Selective Beta-Adrenergic Blockers
ATC Code	C07AA05

Pharmacological Class (ASHP)	Beta-Adrenergic Blocker
DRUG INFORMATION	
Dosage Form	Oral suspension/solution
Route of Administration	Oral
Dose (pediatrics)	***Hemangeol*:** Infants ≥5 weeks and ≥2 kg: Note: Therapy should be initiated at age 5 weeks to 5 months: Oral: Initial dose: 0.6 mg/kg/dose twice daily for 1 week, then increase dose to 1.1 mg/kg/dose twice daily for 1 week, and then increase to a maintenance dose of 1.7 mg/kg/dose twice daily for 6 months; doses should be separated by at least 9 hours. ***Immediate-release formulations*:** Limited data available: Infants and Children <5 years: Oral: Initial: 1 mg/kg/day in 2 or 3 divided doses, increase by 1 mg/kg/day at weekly intervals to maintenance dose; usual daily maintenance dose: 1 to 3 mg/kg/day in 2 or 3 divided doses.
Maximum Daily Dose Pediatrics	N/A
Adjustment	There are no dosage adjustments
Prescribing edits	N/A
AGE (Age Edit):	N/A
CU (Concurrent Use Edit):	N/A
G (Gender Edit):	N/A
MD (Physician Specialty Edit):	N/A
PA (Prior Authorization):	N/A
QL (Quantity Limit):	N/A
ST (Step Therapy):	N/A
EU (Emergency Use Only):	N/A
PE (Protocol Edit):	N/A
SAFETY	
Main Adverse Drug Reactions (most common and most serious)	**>10%:** -Nervous system: Sleep disorder -Respiratory: Bronchiolitis, bronchitis

	1% to 10%: -Cardiovascular: Cold extremity -Gastrointestinal: Abdominal pain, constipation, decreased appetite, diarrhea -Nervous system: Agitation, dizziness, drowsiness, fatigue, irritability, nightmares
Drug Interactions	Category X: • Beta2-Agonists • Brompéridol
Special Population	Infants and children: Considerations when treating IH: -Cardiovascular concerns: Bradycardia and/or hypotension may occur or be worsened. -Hypoglycemia: May potentiate hypoglycemia and/or mask signs and symptoms.
Contraindications	-Hypersensitivity to propranolol, beta-blockers, or any component of the formulation -Uncompensated heart failure -Cardiogenic shock -Severe sinus bradycardia -Bronchial asthma -Premature infants with corrected age <5 weeks and infants weighing <2 kg
Monitoring Requirements	-ECG -Blood Pressure -HR and BP -Infantile hemangioma: *In-person initiation:* Monitor HR and BP at baseline and 1 and 2 hours after initiation of therapy or dose increases *Telemedicine:* Baseline: Weight (within 2 weeks prior to initiation), cardiovascular examination (within 4 weeks prior to initiation) including ≥1

	documentation of HR after nursery discharge
Precautions	***Concerns related to adverse events:*** • Anaphylactic reactions: Use caution with history of severe anaphylaxis to allergens ***Disease-related concerns:*** • Heart failure: Use with caution in patients with compensated heart failure and monitor for a worsening of the condition • Hepatic impairment: Use with caution in patients with hepatic impairment • Myasthenia gravis: Use with caution in patients with myasthenia gravis. • Peripheral vascular disease and Raynaud disease: Can precipitate or aggravate symptoms of arterial insufficiency in patients with peripheral vascular disease and Raynaud disease. • Pheochromocytoma (untreated): Adequate alpha-blockade is required prior to use of any beta-blocker. • Psoriasis: Beta-blocker use has been associated with induction or exacerbation of psoriasis but cause and effect have not been firmly established. • Renal impairment: Use with caution in patients with advanced renal impairment during initiation of therapy, as decreased hepatic extraction may result in elevated propranolol concentrations and increase the risk of side effects. • Thyroid disease: May mask signs of hyperthyroidism (eg, tachycardia). Alterations in thyroid function tests may be observed. • Vasospastic angina: Beta-blockers without alpha-1 adrenergic receptor blocking activity should be avoided in

	patients with vasospastic angina since unopposed alpha-1 adrenergic receptors mediate coronary vasoconstriction and can worsen anginal symptoms.
Black Box Warning	Abrupt withdrawal of this drug may cause exacerbation of angina or a myocardial infarction.
REMS	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of IH treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable. **The recommendations below are for Propranolol.**

Table 10. Propranolol HTA Recommendations

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Propranolol	NICE	N/A
	CADTH[21]	February 2017 The CADTH recommends that propranolol oral solution be reimbursed for the treatment of proliferating IH requiring systemic therapy in the following circumstances: • Life or function-threatening hemangioma • Ulcerated hemangioma with pain and/or lack of response to simple wound care measures • Hemangioma with a risk of permanent scarring or disfigurement if the following condition: Substantial reduction in price.
	HAS	N/A
	IQWIG[22]	August 2014 Propranolol is indicated for the treatment of proliferating IH requiring systemic therapy. Life or function-threatening hemangioma, Ulcerated hemangioma with pain and/or lack of

		response to simple wound care measures: Added benefit not proven. Hemangioma with a risk of permanent scars or disfigurement Indication of a major added benefit. Comparator: Individual treatment. The specifications of the respective SPCs of the drugs used for treatment are to be considered.
	PBAC	N/A

CONCLUSION STATEMENT-Propranolol

Propranolol is indicated for the treatment of proliferating IH requiring systemic therapy in the following circumstances: Life or function-threatening hemangioma, ulcerated hemangioma with pain and/or lack of response to simple wound care measures and hemangioma with a risk of permanent scarring or disfigurement. Therapy should start at a dose of 1.0 mg/kg/day, with cardiovascular assessments conducted before and one and two hours after administering the prescribed dose. If well-tolerated, the propranolol dose can be increased to 2 mg/kg/day the following day. Potential cardiovascular concerns, such as bradycardia and/or hypotension may manifest or become more severe when using propranolol. Additionally, vigilance regarding hypoglycemia is required.

2.2.3 Atenolol

Information on Atenolol is detailed in the table below[23].

Table 11. Atenolol Drug Information

SCIENTIFIC NAME ATENOLOL	
SFDA Classification	Prescription
SFDA	N/A
US FDA	N/A
EMA	N/A
MHRA	N/A
PMDA	N/A
Indication (ICD-10)	D18.0
Drug Class	Beta-Adrenergic Blockers
Drug Sub-class	Selective Beta-1 Adrenergic Blockers
ATC Code	C07AB03

Pharmacological Class (ASHP)	Beta-Adrenergic Blocker
DRUG INFORMATION	
Dosage Form	Tablet
Route of Administration	Oral
Dose (pediatrics)	**Limited data available: Infants and Children <2 years: Oral:** 1 mg/kg/dose once daily for 6 months
Maximum Daily Dose Pediatrics	N/A
Adjustment	**Altered kidney function: Infants, Children, and Adolescents: Oral:** -**GFR 30 to 50 mL/minute/1.73 m²:** Maximum dose: 1 mg/kg/dose every 24 hours; maximum adult daily dose: 50 mg/day -**GFR 10 to <30 mL/minute/1.73 m²:** Maximum dose: 1 mg/kg/dose every 48 hours, maximum dose should not exceed 50 mg/dose -**GFR <10 mL/minute/1.73 m²:** Maximum dose: 1 mg/kg/dose every 48 hours, maximum dose should not exceed 25 mg/dose
Prescribing edits	N/A
AGE (Age Edit):	N/A
CU (Concurrent Use Edit):	N/A
G (Gender Edit):	N/A
MD (Physician Specialty Edit):	N/A
PA (Prior Authorization):	N/A
QL (Quantity Limit):	N/A
ST (Step Therapy):	N/A
EU (Emergency Use Only):	N/A
PE (Protocol Edit):	N/A
SAFETY	
Main Adverse Drug Reactions (most common and most serious)	**>10%:** Cardiovascular: Bradycardia, heart failure, hypotension, supraventricular tachycardia, ventricular tachycardia. **1% to 10%:**

	-Cardiovascular: Atrial fibrillation, atrial flutter, heart block, orthostatic hypotension, pulmonary embolism -Gastrointestinal: Diarrhea, nausea -Nervous system: Dizziness, fatigue, lethargy, vertigo -Respiratory: Bronchospasm
Drug Interactions	Category X: • Beta2-Agonists • Brompéridol
Special Population	Infants and children: Considerations when treating IH: -Cardiovascular concerns: Bradycardia and/or hypotension may occur or be worsened. -Hypoglycemia: May potentiate hypoglycemia and/or mask signs and symptoms.
Contraindications	-Hypersensitivity to atenolol or any component of the formulation -Sinus bradycardia -Heart block greater than first-degree -Cardiogenic shock -Uncompensated cardiac failure
Monitoring Requirements	-BP -HR -Mental alertness -Signs and symptoms of bronchospasm in patients with existing bronchospastic disease -Serum glucose (in patients with diabetes) -Kidney function.
Precautions	***Disease-related concerns:*** • Anaphylaxis: Beta-blockers are unlikely to cause anaphylaxis • Heart failure: Stabilize patients on heart failure regimen prior to initiation or titration of beta-blocker. Beta-blocker therapy should be initiated at very low

	doses with gradual and very careful titration. • Myasthenia gravis: Use with caution in patients with myasthenia gravis. • Peripheral vascular disease and Raynaud disease: May precipitate or aggravate symptoms of arterial insufficiency in patients with Raynaud disease. • Pheochromocytoma (untreated): Adequate alpha-blockade is required prior to use of any beta-blocker. • Psoriasis: Beta-blocker use has been associated with induction or exacerbation of psoriasis, but cause and effect have not been firmly established. • Renal impairment: Use with caution in patients with renal impairment • Thyroid disease: May mask signs of hyperthyroidism (eg, tachycardia). If hyperthyroidism is suspected, carefully manage and monitor.
Black Box Warning	**Cessation of Therapy** Abrupt discontinuation of beta-blockers like atenolol can lead to severe worsening of angina, and it has been associated with cases of myocardial infarction (heart attack) and ventricular arrhythmias in patients with angina. These heart-related complications can occur with or without prior exacerbation of angina symptoms.
REMS	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

A search for clinical economic recommendations from the Health Technology Assessment (HTA) bodies didn't yield any guidance for Atenolol in IH.

CONCLUSION STATEMENT-Atenolol

Atenolol is an effective alternative treatment for IH. Its hydrophilic nature suggests a reduced likelihood of central nervous system side effects. The usual recommended dose is 1 mg/kg/dose once daily for 6 months. Potential cardiovascular concerns, such as bradycardia and/or hypotension may manifest or become more severe when using atenolol. Additionally, vigilance regarding hypoglycemia is required. There are no recommendations issued by the HTA bodies for Atenolol in this indication.

Section 3.0 Key Recommendations Synthesis

IHs are the most prevalent benign soft-tissue tumors that occur during infancy. These growths predominantly affect female, preterm, and low-birth weight infants, typically appearing within the first few weeks of life. They tend to grow rapidly during infancy but often undergo spontaneous regression over the course of months or yearss. While most IHs do not pose clinical issues, around 10%–15% are linked to problems such as obstruction, ulceration, cosmetic deformities, and, in some cases, life-threatening complications, necessitating proactive treatment. The choice of treatment for IHs varies depending on factors like the child's age, tumor characteristics (location, size, depth), the presence of complications, and the preferences of healthcare providers and family members. Accepted international treatment methods encompass oral medications, topical treatments, intralesional injection therapy, laser therapy, and surgical excision.

Oral medications

- Propranolol hydrochloride in oral solution, is highly recommended as the primary treatment for IH in cases of severe complications, functional limitations, ulceration, or structural anomalies like PHACE or LUMBAR syndrome, or when the condition leads to lasting disfigurement **(Level A; strong recommendation).**
- The recommended dosage is 1 to 3 mg/kg given twice daily. There may be necessary dose adjustments for premature infants or those with poor growth **(Level A; strong recommendation).**
- The lipophilic nature of Propranolol raises concerns about potential neurodevelopmental or cognitive side effects **(Level X; strongly recommended).**
- Initial findings suggest that hydrophilic beta blockers like nadolol and atenolol may be as effective as propranolol for IH treatment. Their hydrophilicity suggests a lower likelihood of central nervous system side effects.
- Retrospective studies favor oral propranolol over corticosteroid treatment for IH, showing it leads to fewer surgeries and has better tolerance with minimal side effects **(Level B; moderate recommendation).**
- Oral corticosteroids may still be an option for complicated IH cases not responsive to propranolol, or for patients with contraindications or side effects.
- Corticosteroids like prednisolone are recommended as a second-line therapy. The recommended dosage ranges from 2 to 5 mg/kg per day for 4 to 12 weeks, followed by a gradual taper over 9 to 12 months.

- A proposed approach suggests using low-dose corticosteroids alongside propranolol for segmental hemangiomas in PHACES syndrome with cerebral vascular involvement.

Topical treatments

- Topical beta blockers show promise as a treatment for IH, with propranolol and timolol being the most effective options based on case reports.
- Timolol maleate 0.5% in topical form is moderately recommended for the management of thin and/or superficial IHs, with a dosage of one drop twice daily **(Level B; moderate recommendation).**
- The systemic absorption and potential side effects of these topical drugs haven't been thoroughly studied in infants, especially around the eye where absorption through the conjunctiva is a concern.
- Until more systematic studies confirm their safety and effectiveness, topical beta blockers shouldn't be the standard IH therapy.
- However, they could potentially become the first-line treatment for small, superficial IH in problematic areas, reducing the need for systemic treatment in many IH cases.

Intralesional injection

- Intralesional corticosteroid injections are recommended for specific cases of proliferating IHs, particularly those in early stages, limited in extent, deep-seated, or significantly protruding from the body surface **(Level B, moderate recommendation).**
- Intralesional injections of Triamcinolone and/or Betamethasone are moderately recommended, with dosages ranging from 1 to 2 mg/kg per dose every 4 to 6 weeks or 1.5 to 18 mg/dose every 8 to 14 weeks, respectively.
- Triamcinolone acetonide, being a smaller molecule with lower activity compared to betamethasone, may carry a reduced risk of adverse effects such as thrombosis.
- Safety considerations for local corticosteroid injections include potential local skin effects like hypopigmentation, subcutaneous lipoatrophy, and local ulceration. Systemic effects may involve a Cushing-like appearance, developmental growth arrest, and adrenal suppression **(Level B; moderate recommendation).**

Laser therapy

- Administering pulsed-dye laser therapy in the early stages can offer benefits for flat hemangiomas.
- Additionally, laser treatment may prove effective for ulcerated lesions that do not show improvement with suitable dressings.

Surgical excision

- Traditional view held surgery as essential for managing complicated IH.
- Cryosurgery might be an option in certain cases, but its use relies heavily on empirical evidence.
- Conventional surgery is advised in extremely rare instances of hemangiomas resistant to propranolol or in emergencies. It also serves a crucial role in post-resolution reconstruction, addressing excess skin and residual scarring (**Level C, moderate recommendation)**

Section 4.0 Conclusion

The recommendations provided in this report are intended to assist in the management of IHs.

These recommendations should be used to support and not supplant decisions in individual patient management.

Section 5.0 References

1. Chamli A, Aggarwal P, Jamil RT, Litaiem N. Hemangioma. *Bone Tumors: Diagnosis and Therapy Today*. Published online June 12, 2023:115-116. doi:10.1007/978-1-4471-7501-8_13
2. Krowchuk DP, Frieden IJ, Mancini AJ, et al. Clinical practice guideline for the management of infantile hemangiomas. *Pediatrics*. 2019;143(1). doi:10.1542/PEDS.2018-3475/37268
3. Al-Jazaeri A. The response pattern and adherence to oral propranolol among Saudi children treated for infantile hemangioma. *Journal of Dermatology & Dermatologic Surgery*. 2017;21(1):1-6. doi:10.1016/J.JDDS.2016.10.002
4. Fatani M, otaibi H Al, Alshareef M, Khalifa M, Mohammed S. A Retrospective Study of Infantile Hemangiomas: Demographic and Clinical Characteristics at Hera General Hospital, Makkah, Saudi Arabia. *J Pigment Disord*. 2018;05(01). doi:10.4172/2376-0427.1000270
5. Solman L, Glover M, Beattie PE, et al. Oral propranolol in the treatment of proliferating infantile haemangiomas: British Society for Paediatric Dermatology consensus guidelines. *British Journal of Dermatology*. 2018;179(3):582-589. doi:10.1111/BJD.16779
6. Chang L, Lv D, Yu Z, et al. Infantile hemangioma: factors causing recurrence after propranolol treatment. *Pediatr Res*. 2018;83(1):175-182. doi:10.1038/pr.2017.220
7. Frongia G, Byeon JO, Mehrabi A, Günther P. Recurrence rate of infantile hemangioma after oral propranolol therapy. *Eur J Pediatr*. 2021;180(2):585-590. doi:10.1007/s00431-020-03872-5
8. Hoeger PH, Harper JI, Baselga E, et al. Treatment of infantile haemangiomas: recommendations of a European expert group. *Eur J Pediatr*. 2015;174(7):855-865. doi:10.1007/S00431-015-2570-0
9. Alasmari B, Alkhenaizan A, Al-Khenaizan S. Hyperkalemia due to topical timolol for hemangioma. *JAAD Case Rep*. 2023;39:53-54. doi:10.1016/j.jdcr.2023.07.006
10. Muñoz-Garza FZ, Ríos M, Roé-Crespo E, et al. Efficacy and Safety of Topical Timolol for the Treatment of Infantile Hemangioma in the Early Proliferative Stage: A Randomized Clinical Trial. *JAMA Dermatol*. 2021;157(5):1. doi:10.1001/JAMADERMATOL.2021.0596
11. Krowchuk DP, Frieden IJ, Mancini AJ, et al. Clinical practice guideline for the management of infantile hemangiomas. *Pediatrics*. 2019;143(1). doi:10.1542/PEDS.2018-3475/37268

12. Smithson SL, Rademaker M, Adams S, et al. Consensus statement for the treatment of infantile haemangiomas with propranolol. *Australas J Dermatol*. 2017;58(2):155-159. doi:10.1111/AJD.12600

13. Kleinman EP, Blei F, Adams D, Greenberger S. Sirolimus for diffuse intestinal infantile hemangioma with PHACE features: systematic review. *Pediatr Res*. 2023;93(6):1470-1479. doi:10.1038/s41390-022-02325-z

14. Chen T, Gudipudi R, Nguyen SA, Carroll W, Clemmens C. Should Propranolol Remain the Gold Standard for Treatment of Infantile Hemangioma? A Systematic Review and Meta-Analysis of Propranolol Versus Atenolol. *Ann Otol Rhinol Laryngol*. 2023;132(3):332-340. doi:10.1177/00034894221089758

15. Huang H, Chen X, Cai B, Yu J, Wang B. Comparison of the efficacy and safety of lasers, topical timolol, and combination therapy for the treatment of infantile hemangioma: A meta-analysis of 10 studies. *Dermatol Ther*. 2022;35(12):e15907. doi:10.1111/dth.15907

16. Prednisone: Drug information - UpToDate. Accessed September 11, 2023. https://ezproxy.usj.edu.lb:2071/contents/prednisone-drug-information?search=prednisone&source=panel_search_result&selectedTitle=1~148&usage_type=panel&kp_tab=drug_general&display_rank=1#F213103

17. Betamethasone (systemic): Drug information - UpToDate. Accessed October 28, 2023. https://www.uptodate.com/contents/betamethasone-systemic-drug-information?search=betamethasone&source=panel_search_result&selectedTitle=1~120&usage_type=panel&showDrugLabel=true&display_rank=1

18. Timolol (ophthalmic): Drug information - UpToDate. Accessed October 26, 2023. https://www.uptodate.com/contents/timolol-ophthalmic-drug-information?search=timolol%20&source=panel_search_result&selectedTitle=1~44&usage_type=panel&showDrugLabel=true&display_rank=1#F45525781

19. Infantile haemangioma: topical timolol Evidence summary Key points from the evidence. Published online 2015. Accessed October 26, 2023. www.nice.org.uk/guidance/esuom47

20. Propranolol: Drug information - UpToDate. Accessed October 27, 2023. https://ezproxy.usj.edu.lb:2071/contents/propranolol-drug-information?search=propranolol&source=panel_search_result&selectedTitle=1~148&usage_type=panel&kp_tab=drug_general&display_rank=1#F214926

21. Common Drug Review CADTH CANADIAN DRUG EXPERT COMMITTEE FINAL RECOMMENDATION PROPRANOLOL ORAL SOLUTION (Hemangiol-Pierre Fabre Dermo-Cosmétique Canada Inc.) Indication: Infantile Hemangioma Requiring Systemic Therapy. Published online 2017.

22. for Quality I, in Health Care E. Extract 1 Translation of Sections 2.1 to 2.6 of the dossier assessment Propranolol-Nutzenbewertung gemäß § 35a SGB V Propranolol-Benefit assessment according to §35a Social Code Book V 1. Accessed October 27, 2023. www.iqwig.de

23. Atenolol: Drug information - UpToDate. Accessed October 27, 2023. https://ezproxy.usj.edu.lb:2071/contents/atenolol-drug-information?sectionName=Pediatric&topicId=8940&search=atenolol&usage_type=panel&anchor=F137451&source=panel_search_result&selectedTitle=1~108&showDrugLabel=true&kp_tab=drug_general&display_rank=1#F137451

Section 6.0 Appendices

Appendix A. Prescribing Edits Definition

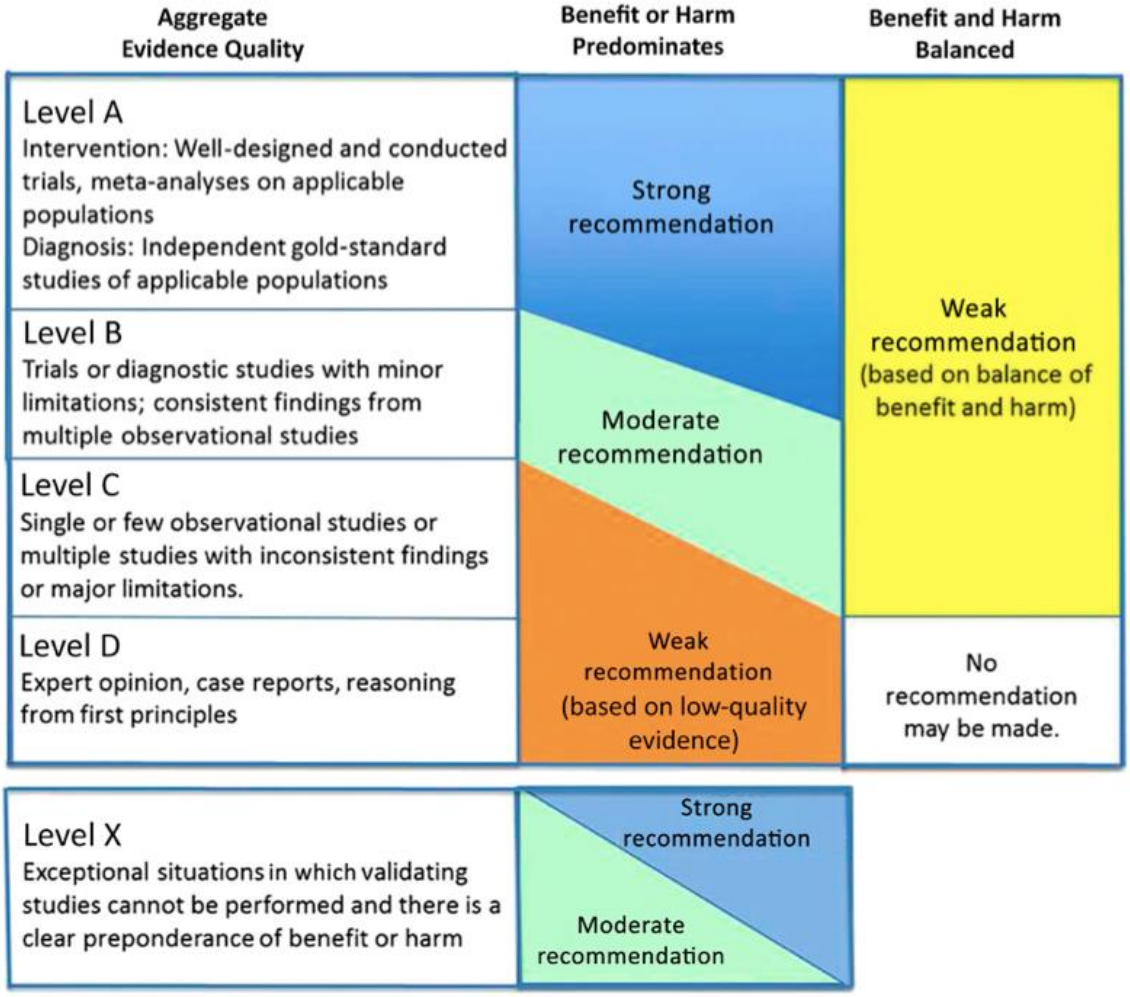
Some covered drugs may have additional requirements, rules or limits on coverage. These requirements and limits may include:

Prescribing edits Tools	Description
AGE (Age):	Coverage may depend on patient age
CU (Concurrent Use):	Coverage may depend upon concurrent use of another drug
G (Gender):	Coverage may depend on patient gender
MD (Physician Specialty):	Coverage may depend on prescribing physician's specialty or board certification
PA (Prior Authorization):	Requires specific physician request process
QL (Quantity Limits):	Coverage may be limited to specific quantities per prescription and/or time period
ST (Step Therapy):	Coverage may depend on previous use of another drug
EU (Emergency Use only):	This drug status on Formulary is only for emergency use
PE (Protocol Edit):	Use of drug is dependent on protocol combination, doses and sequence of therapy

Appendix B. PubMed Search Methodology Terms

Query	Filters	Search Details	Results
((capillary hemangioma[MeSH Terms]) OR (Neoplastic Syndromes, Hereditary[Title/Abstract])) OR (Hemangioma, Capillary[Title/Abstract])	in the last 5 years	("hemangioma, capillary"[MeSH Terms] OR "neoplastic syndromes hereditary"[Title/Abstract] OR "hemangioma capillary"[Title/Abstract]) AND (y_5[Filter])	588

Appendix C. Level of Evidence



Statement	Definition	Implication
Strong recommendation	A particular action is favored because anticipated benefits clearly exceed harms (or vice versa), and quality of evidence is excellent or unobtainable.	Clinicians should follow a strong recommendation unless a clear and compelling rationale for an alternative approach is present.
Moderate recommendation	A particular action is favored because anticipated benefits clearly exceed harms (or vice versa), and the quality of evidence is good but not excellent (or is unobtainable).	Clinicians would be prudent to follow a moderate recommendation but should remain alert to new information and sensitive to patient preferences.
Weak recommendation (based on low-quality evidence)	A particular action is favored because anticipated benefits clearly exceed harms (or vice versa), but the quality of evidence is weak.	Clinicians would be prudent to follow a weak recommendation but should remain alert to new information and sensitive to patient preferences.
Weak recommendation (based on balance of benefits and harms)	A weak recommendation is provided when the aggregate database shows evidence of both benefit and harm that appears to be similar in magnitude for any available courses of action.	Clinicians should consider the options in their decision-making, but patient preference may have a substantial role.

X

Appendix D. Treatment Algorithm of IHs

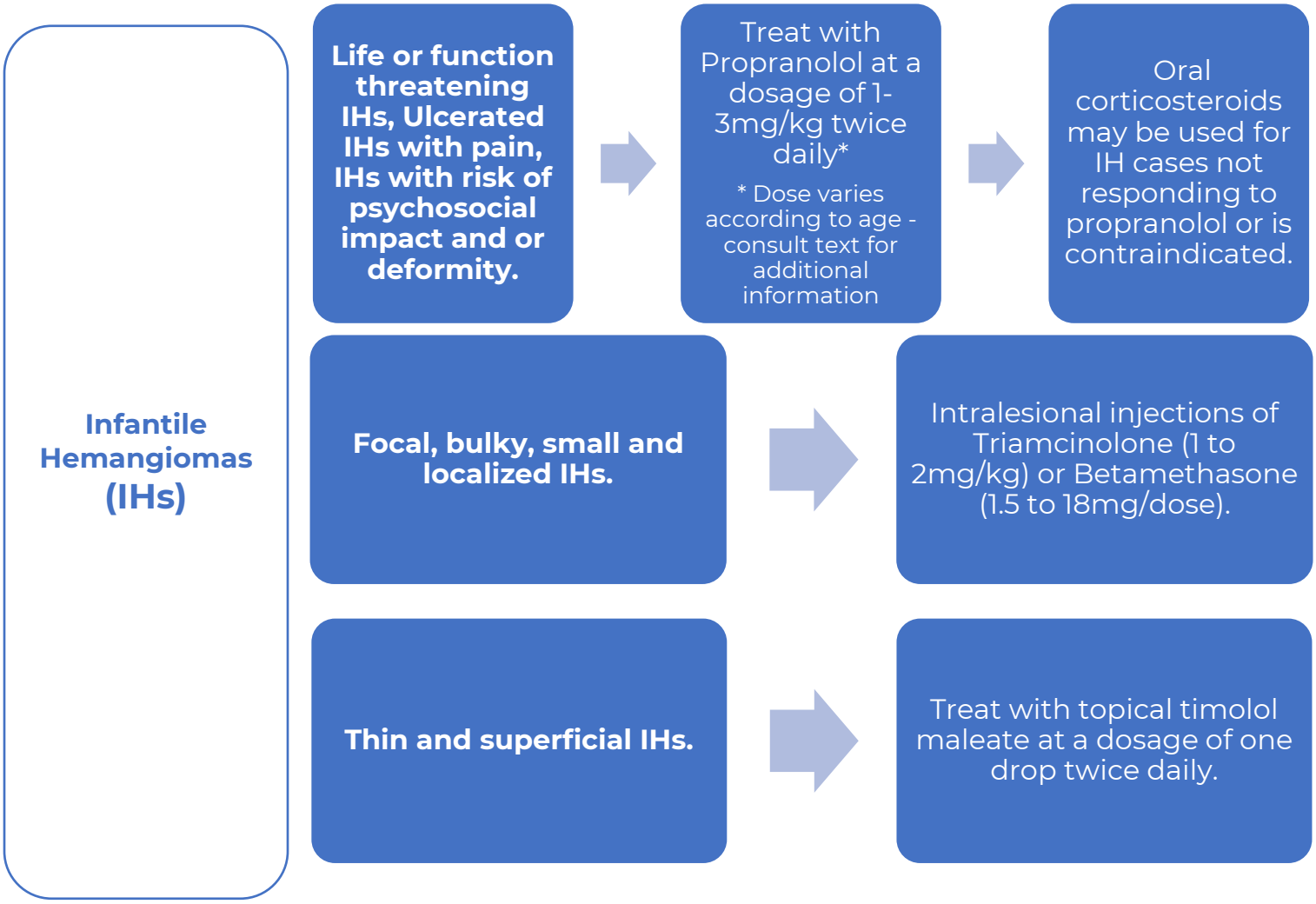


Figure 4. *Treatment algorithm for the management of infantile hemangiomas*