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REVIEW ARTICLE

Medical Management of Infantile Hemangiomas: An Update

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Abstract
Infantile hemangioma (IH) is the most common benign vascular tumor of infancy, affecting about 5% of infants. It has a characteristic growth pattern of early rapid proliferation followed by progressive involution. Although most IH evolve favorably, complications are observed in 10–15% of cases, justifying treatment. For over 10 years now, propranolol has become the first-line therapy for complicated IH, revolutionizing their management and their prognosis. In this article, we review the clinical features, associations, complications/sequelae and therapeutic approaches for IH, focusing on current medical therapy. Indications for treatment and various treatment options, including propranolol and other oral β-blockers, topical timolol, and corticosteroids are presented. Current controversies regarding oral propranolol such as pre-treatment screening, in- vs out-patient initiation of treatment, early and potential long-term side effects and recommended monitoring are discussed.

Key Points

Infantile hemangiomas (IH) are common (4.5% of neonates) and have a characteristic growth and regression pattern, with 80% of the total growth reached by the age of 4 months. The majority of IH have regressed by the age of 4 years.

Associations exist and are important to exclude, like subglottic IH associated with IH of the beard region, PHACES syndrome, and LUMBAR syndrome.

Some complications (disfigurement, functional impairment) can be prevented by an appropriate treatment and oral propranolol is currently the first-line therapy in the treatment of IH. Ulcerated IH necessitate special treatment considerations.

1 Introduction

Infantile hemangiomas (IH) are the most common benign tumors of infancy, with a prevalence estimated at 4.5% [1]. The prevalence is increased in females, Caucasians, preterm or low-weight newborns and twins. It is typically absent at birth (or presents with a precursor lesion such as telangiectasias or an erythematous macule) and arises during the first weeks of life, with a period of active growth before a slow regression. Most IH regress spontaneously without complication. However, complications are observed in 10–15% of hemangiomas [2], justifying treatment. Those complications include disfigurement, functional impairment, ulceration and/or bleeding, and rarely life-threatening situations. Medical treatment is the mainstay in IH treatment, with β-adrenergic blockers, especially propranolol, being widely used. The American Academy of Pediatrics (AAP) published guidelines for the management of IH in 2019 [3]. In this article, we review the highlights of the medical management of IH.

2 Background

2.1 Pathogenesis

The pathogenesis of IH is not yet fully elucidated, but it is believed that IH originate from the formation of blood vessels by fetal immature progenitor cells, capable to

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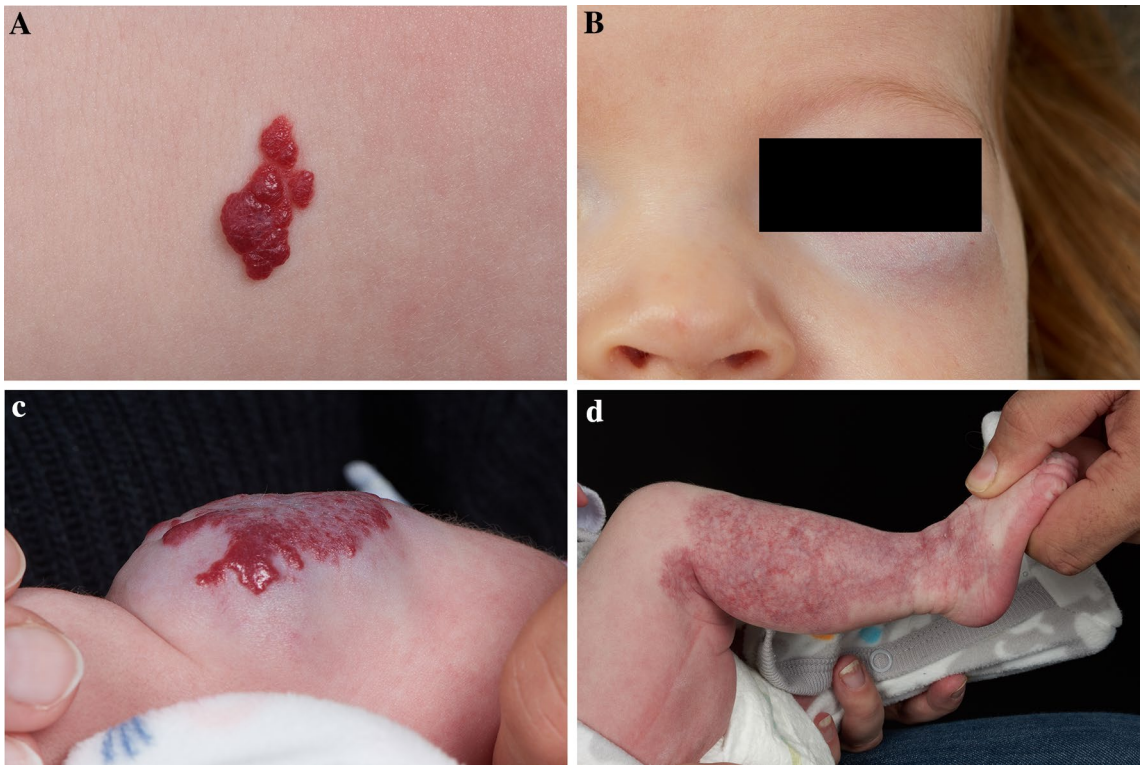

Fig. 1 Clinical subtypes of infantile hemangioma (IH). **A** Superficial IH. **B** Deep IH. **C** Mixed IH. **D** Abortive IH (at 4 months of age)

differentiate into endothelial cells, pericytes, dendritic cells, and adipocytes. During the proliferative phase, the environment promotes the differentiation towards endothelial cells and pericytes, while in the regression phase, it switches to promote the differentiation into adipocytes. The recruitment and proliferation of those progenitor cells are stimulated by proteins such as vascular endothelial growth factor (VEGF) and matrix metalloproteinases (MMP) 2 and 9 [2, 4] which are regulated by β-adrenergic blockers [5]. The trigger that initiates the recruitment of the endothelial progenitor cells is still uncertain, but the most likely theory is that hypoxic stress acts as the initiator of the overproduction of the angiogenic factors [2]. Glucose transport protein-1 (GLUT-1) is expressed in every step of IH maturation and allows the histologic diagnosis if needed.

2.2 Epidemiology

The prevalence of IH is around 4.5% of mature neonates, with higher risk in Caucasians and females. Other known risk factors are prematurity, low birthweight, family history of IH, intrauterine complications (such as eclampsia), placental anomalies, and twin pregnancy [2, 6].

2.3 Clinical Features

The clinical course of IH is typical: precursor lesions are present at birth (in half of the patients [7]) or in the first few days of life; it can be either telangiectasias, an erythematous macule, or an area of vasoconstriction. The proliferative phase starts after 1–3 weeks of latency: the growth is rapid during the first 3 months, and about 80% of the total growth is reached by the age of 4 months [8]. It has been shown that the optimal time for referral or initiation of treatment (if needed) is 1 month of age [9]. The growth phase can last longer in deep IH, until the 9th to 12th months, up to 24 months in rare cases. After a short period of stability, slow spontaneous regression is observed, and is completed by the age of 4 years in most cases [2, 10–12]. Cases of late growth after 3 years of age have been described. Risk factors include head and neck location, segmental morphology and involvement of deep dermal/subcutaneous tissues [13]. IH can be (1) superficial (Fig. 1A), with proliferation arising in the dermis, (2) deep (Fig. 1B), with proliferation localized in the hypodermis, (3) mixed (Fig. 1C), with a superficial and a deep component in the same lesion, or (4) abortive/minimal growth (Fig. 1D). Superficial IH present as red papules, nodules, or plaques. They are tense and bright, dark red during the proliferative phase, and become dull, greyish,

and soft during the regression phase. Deep IH present as a subcutaneous mass with or without a bluish color. They are firm and elastic in consistency in the proliferative phase, then become soft during the regression phase. Abortive/minimal growth IH present as a telangiectatic macule with small, superficial papules. In terms of pattern, IH can be focal (Fig. 2A) (when it seems to arise from a central focal point), multifocal (Fig. 2B), or segmental (Fig. 2C) (when it covers an anatomic territory). When IH is neither clearly focal nor segmental, it is called indeterminate [3].

2.4 Association/Syndromes/Complications

Table 1 summarizes potential complications, associations and syndromes involving IH.

Two syndromes are recognized with segmental IH: PHACES syndrome (Posterior fossa malformation, Hemangioma (Fig. 3A), Arterial anomalies, Cardiovascular anomalies, Eye anomalies, Sternal clefting/Supraumbilical raphe) and LUMBAR syndrome (Lower body hemangioma (Fig. 3B), Urogenital anomalies, Myelopathy, Bony deformities, Anorectal malformations, Arterial anomalies and Renal anomalies). There are also other acronyms used such as SACRAL syndrome (Spinal dysraphism, Anogenital, cutaneous and Renal anomalies, hemAngioma in the Lumbar region) [14] or PELVIS syndrome (Perineal hemangioma, External genitalia malformations, Lipomyelomeningocele, Vesicorenal abnormalities, Imperforate anus, and Skin tag) [15].

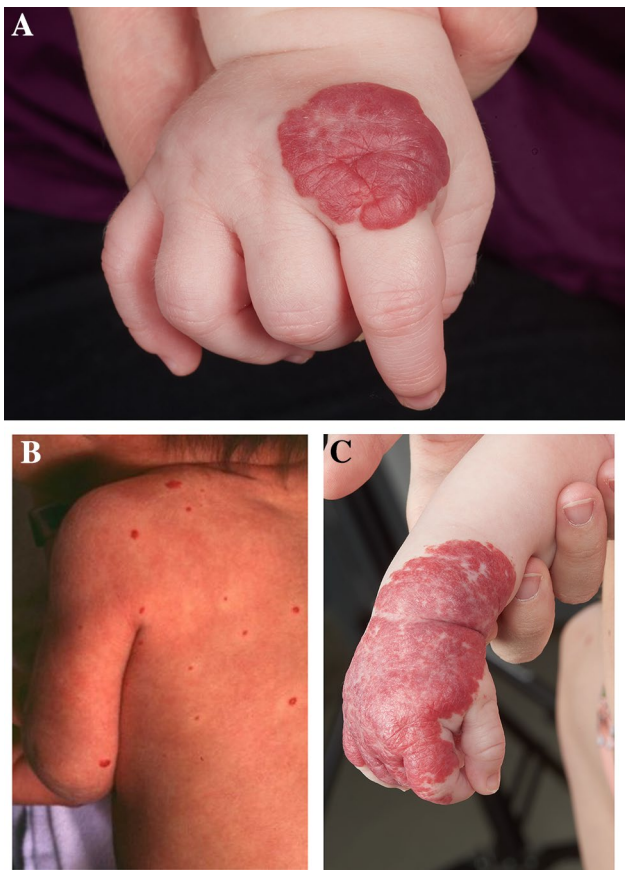

Fig. 2 Patterns of infantile hemangioma (IH). **A** Focal IH. **B** Multifocal IH, **C** segmental IH

Two situations are life-threatening. IH of the beard region/mandibular (S3) (Fig. 3C) (chin, lower lip, lower gum, preauricular area and anterior neck) can be associated with obstructive airways hemangioma (subglottic IH), especially if involvement is bilateral [16]. Multiple IH, defined as $\geq$ 5 IH, can be associated with intra-hepatic IH, cardiac failure, hypothyroidism, and, rarely, compartment syndrome [3, 17].

Ulceration is one of the most frequent complications [7], occurring in about 15% of IH. It concerns mainly large, superficial, and segmental IH (Fig. 4), and IH localized in the head and neck region, the intertriginous areas, or in the perineal and buttock region, during the rapid proliferation phase [18, 19]. In a recent retrospective study, the median age of ulceration was 13.7 weeks with most developing by age 4 months [18, 19].

Other complications can be either functional or aesthetic. Infants with IH of the periocular region are at risk of astigmatism, amblyopia, or strabismus. IH of the lips can impair feeding in the infant and often ulcerate.

More than half of untreated IH leave sequelae. The most common sequelae are telangiectasias (Fig. 5A), fibrofatty tissue (Fig. 5B), and anetodermic skin. Less frequent are redundant skin and scarring (Fig. 5C) (in ulcerated IH). The IH characteristics correlate with the type of sequelae; sequelae are more frequent in mixed IH, and with IH that have a stepped border or a cobblestoned surface of the superficial component [7, 10].

Rarely, obstruction of the nostrils or auditory channel is observed, or positional torticollis due to a large IH of the neck [2].

3 Who Needs a Workup?

The diagnosis of IH is clinical. Doppler ultrasound is a valuable, effective, and minimally invasive exam for confirming the diagnosis in case of doubt. If doubt persists, a biopsy with GLUT1 staining may be needed, particularly if a malignant tumor or another vascular tumor is a possible diagnosis. Nevertheless, ultrasonography depends on the experience of the radiologist, and cannot define the extension of the tumor. Magnetic resonance imaging (MRI) is better to delineate the extent of the lesion. Computed tomography (CT) is less often used [20].

Table 1 Complications, associations, and syndromes involving infantile hemangiomas (IH) [3]

Complications/association/syndrome	Comment
SYNDROMES	
PHACES	Associated with segmental IH of the face/neck/scalp
LUMBAR/SACRAL/PELVIS	Associated with segmental lumbosacral IH
LIFE-THREATENING SITUATIONS	
Obstructive airway hemangioma	Associated with IH of the beard region/bilateral S3
Intrahepatic IH (if diffuse)	Risk of cardiac failure, hypothyroidism, compartment syndrome
ULCERATION	15% of IH; mainly before 4 months of age
FUNCTIONAL COMPLICATIONS	
Ocular complications: astigmatism, amblyopia, strabismus	IH of the periocular region
Feeding disabilities	IH of the oral cavity
Obstruction of the nostrils or auditory channels	IH of nose or ear
Positional torticollis	IH of the neck
AESTHETIC COMPLICATIONS/DISFIGUREMENT	More frequent in mixed IH and in IH with a stepped border or a cobblestone surface
Telangiectasias	
Fibrofatty tissue	
Anetodermic skin	
Redundant skin	
Scarring	Ulcerated IH
Deformation of cartilage	IH of the nose or ears

PHACES PHACES syndrome (Posterior fossa malformation, Hemangioma, Arterial anomalies, Cardiovascular anomalies, Eye anomalies, Sternal clefting/Supraumbilical raphe), *LUMBAR* LUMBAR syndrome (Lower body hemangioma, Urogenital anomalies, Myelopathy, Bony deformities, Anorectal malformations, Arterial anomalies and Renal anomalies), *SACRAL* SACRAL syndrome (Spinal dysraphism, Anogenital, Cutaneous and Renal anomalies, hemAngioma in the Lumbar region), *PELVIS* PELVIS syndrome (Perineal hemangioma, External genitalia malformations, Lipomyelomeningocele, Vesicorenal abnormalities, Imperforate anus, and Skin tag)

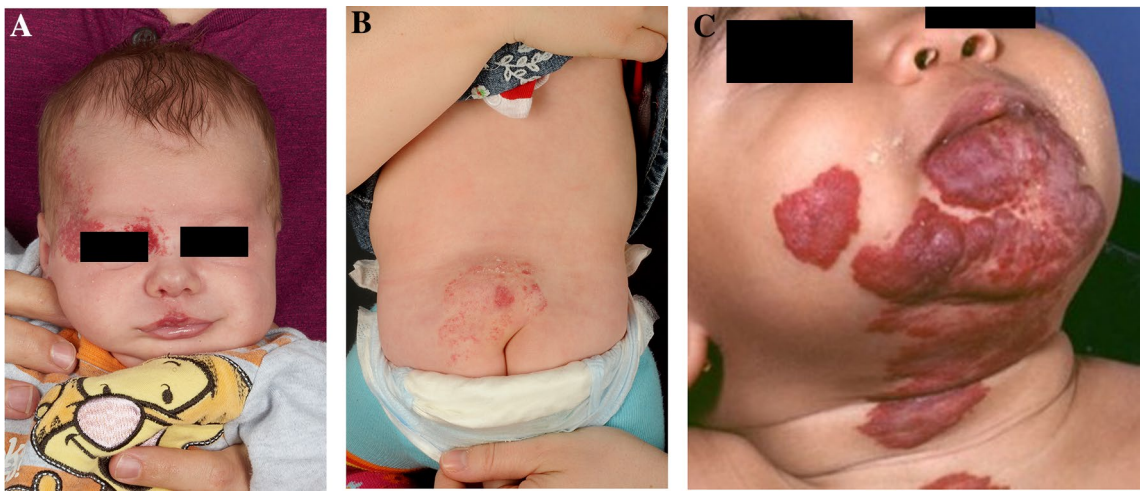

Fig. 3 Syndromal infantile hemangioma (IH). **A** PHACES syndrome (posterior fossa malformation, hemangioma, arterial anomalies, cardiovascular anomalies, eye anomalies, sternal clefting/supraumbilical raphe). **B** LUMBAR syndrome (lower body hemangioma, urogenital anomalies, myelopathy, bony deformities, anorectal malformations, arterial anomalies and renal anomalies). **C** Beard IH

Table 2 presents the five major indications for considering treatment and/or further evaluation according to the AAP guidelines [3].

In the of case of segmental IH of the beard region, early referral to the otolaryngologist with endoscopic airway examination is suggested to exclude the risk of subglottic IH [16].

In case of multiple cutaneous IH (≥ 5) [17], an abdominal ultrasound with doppler is recommended. The hepatic lesions can have serious complications such as cardiac

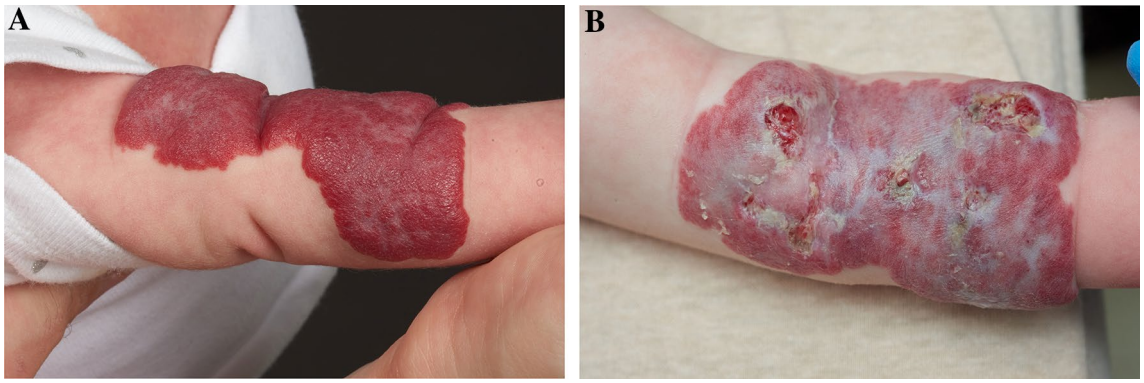

Fig. 4 Ulcerated infantile hemangioma (IH). **A** Large segmental IH of the arm at 4 weeks of life. **B** Ulcerated segmental IH at 4 months of life

failure or severe hypothyroidism, which are important to exclude if the hepatic involvement is diffuse or multifocal. Abdominal ultrasound and screening of thyroid function are needed at diagnosis and should be repeated according to findings and clinical evolution [21]. However, a recent study showed that among more than 800 patients with IH, more than a third with hepatic IH had fewer than five cutaneous IH, all cases of cardiac failure had clinical symptoms/signs at first presentation, and almost all cases of hypothyroidism were detected by neonatal screening. Therefore, the authors' recommendation is to base the use of abdominal ultrasound on clinical signs/symptoms of cardiac failure [22].

Imaging is essential if there is a risk of PHACES or LUMBAR syndrome. In case of segmental IH of the face, neck, or scalp, an MRI/MRA (magnetic resonance angiography) of the head and neck and aortic arch is required, along with a careful cardiac evaluation including echocardiography and an ophthalmological evaluation. Careful periodic developmental and neurological assessments will be needed. In segmental IH of the perineum, gluteal cleft, or lumbosacral area, an MRI of the spine and a doppler ultrasonography of the abdomen should be performed. Alternatively, patients < 6 months of corrected age could benefit from a spinal ultrasonography and doppler ultrasonography of the abdomen, but MRI will likely be needed eventually for a better definition [3].

Hemangioma of the orbital region should be referred to the ophthalmologist for evaluation and joint follow-up.

4 Who Needs Treatment?

Most IH are small and tend to regress spontaneously without need for intervention and can be managed with a 'watchful waiting' approach. Education of the family about the natural evolution of IH and prognosis is important.

Treatment is required for complicated cases, including life-threatening IH, IH causing functional impairment, ulcerated IH, and IH susceptible to causing disfigurement [2, 23]. Given the evolutive profile of IH, there is a window of opportunity for treatment; early referral and treatment is important to target the proliferation phase and for optimal results.

Recently, a group of experts developed the Infantile Hemangioma Referral Score (IHReS) screening tool to facilitate the early and appropriate referral to expert centers [24]. They also recommend frequent reassessment by non-expert practicians if the IHReS is initially too low to justify a referral: it is suggested that the frequency of monitoring visits (in weeks) should be equal to the age of the infant (in months).

The aim of the treatment is arresting growth, hastening involution, and preventing or minimizing sequelae.

5 Which Treatment to Use?

5.1 Systemic Treatment

5.1.1 Propranolol

Since the first publication of Léauté-Labrèze et al. in 2008 reporting the initial series of 11 children who displayed a cessation of growth and regression of IH while taking propranolol [25], more and more evidence of the efficacy of propranolol in the treatment of IH has been gathered, and it has quickly become the treatment of choice for IH. A pivotal multicenter prospective trial confirmed its efficacy and safety [26]. Propranolol is currently the only US Food and Drug Administration (FDA)/European Medicines Agency (EMA)-approved treatment for complicated IH.

The mechanism of action of propranolol in IH is still unclear but is probably multifactorial; it seems to act as a vasoconstrictor in the lesion, inhibit vasculogenesis and angiogenesis, induce apoptosis of hemangioma-derived endothelial cells, regulate the renin-angiotensin system and inhibit nitric oxide production [3, 5].

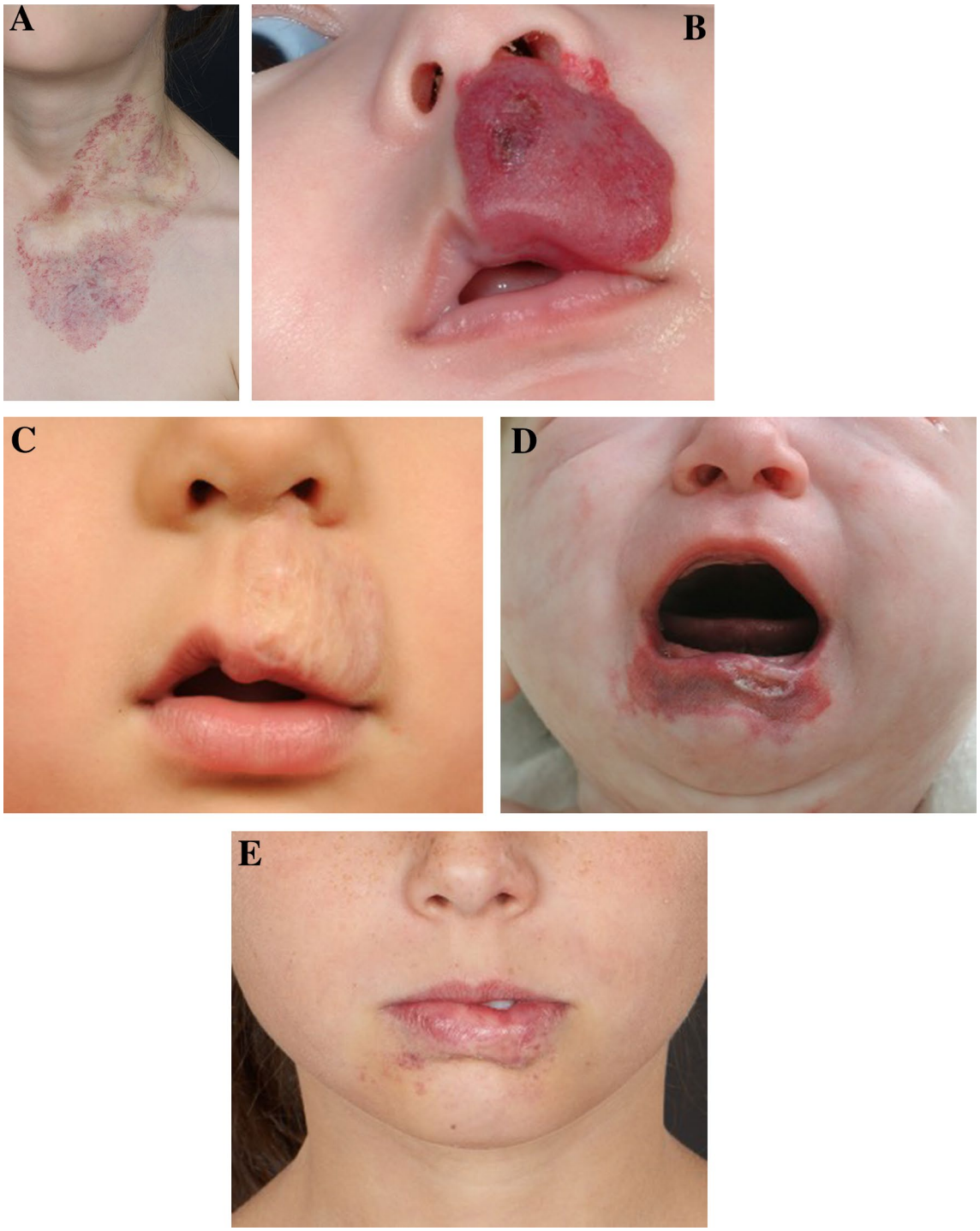

Fig. 5 Sequelae of infantile hemangioma (IH). **A** Telangiectasias and central scarring at 7 years of age. This patient benefited from oral propranolol from 2 to 24 months, and PDL at 9 years old. **B** IH of the upper lip at 3 months old leading to **C** fibrofatty tissue at 4 years of age after two surgical resections and seven sessions of PDL. **D** Ulcerated IH of the lower lip at 5 weeks of age leading to **E** scarring at 10 years of age. *PDL* pulsed dye laser

Oral propranolol hydrochloride (Hemangeol®, Pierre Fabre Dermatologie, Lavaur, France) was approved by the US FDA in March 2014 for proliferating IH requiring systemic therapy and is now the first-line therapy in the treatment of IH, with an excellent benefit–risk profile. Several randomized trials [26–28] have shown the efficacy of propranolol at doses of 2–3 mg/kg/day, and a complete or nearly complete regression in 60% of cases after 6 months'

Table 2 Major indications for considering treatment and/or further evaluation according to the AAP guidelines

Risk of life-threatening complications: obstructive IH of the airways, liver IH associated with congestive heart failure or severe hypothyroidism, and profuse bleeding from an ulcerated IH (extremely rare)
Risk of associated structural anomalies (PHACE and LUMBAR syndromes)
(Risk of) functional impairment
(Risk of) ulceration
Risk of leaving permanent scarring/disfiguration

PHACES syndrome (Posterior fossa malformation, Hemangioma, Arterial anomalies, Cardiovascular anomalies, Eye anomalies, Sternal clefting/Supraumbilical raphe), LUMBAR syndrome (Lower body hemangioma, Urogenital anomalies, Myelopathy, Bony deformities, Anorectal malformations, Arterial anomalies and Renal anomalies)

AAP American Academy of Pediatrics, *IH* Infantile hemangioma

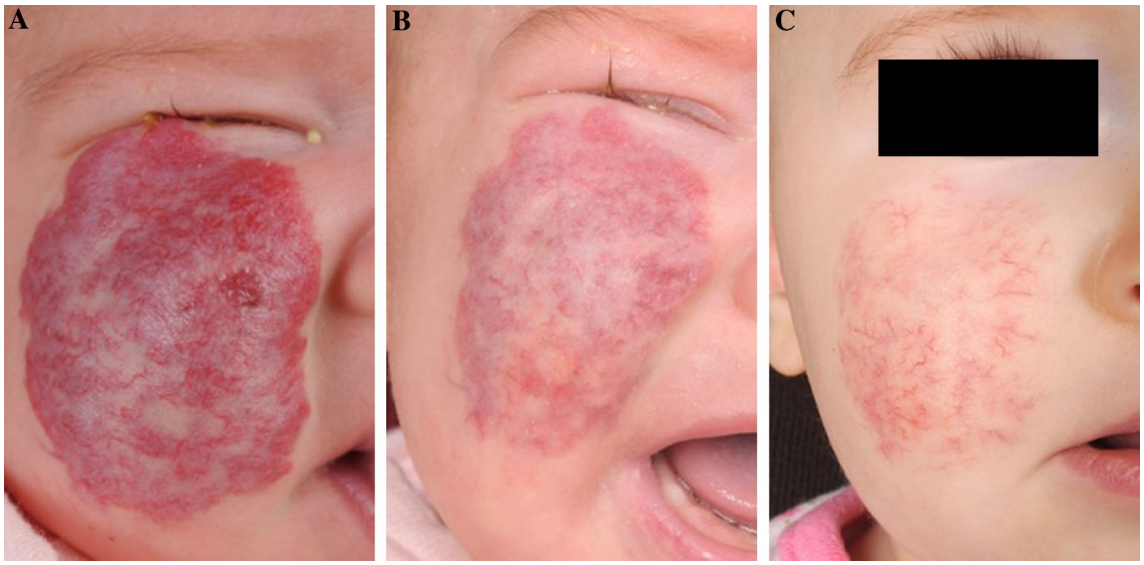

Fig. 6 Evolution of infantile hemangioma (IH) under oral propranolol (2 mg/kg/day, adjusted to body weight). **A** At initiation of treatment (2 months of age); **B** 1 month after initiation (3 months of age); **C** 6 months after initiation (8 months of age)

treatment. In a 2013 meta-analysis of 1264 patients, oral propranolol was introduced at a mean age of 6.6 months at a mean dose of 2.1 mg/kg/day, and the response rate was 98% [29]. In most of the patients receiving propranolol, a change in color (from intense red to dull purple) and softening of the lesion can be noticed as soon as 24 h after introduction of treatment. Progressive reduction of redness, softening, and decrease in thickness of the lesion is then observed (Fig. 6) [30].

There is better efficacy of propranolol if it is introduced before the end of the growth phase, and the earlier in the growth phase the better for the functional and/or aesthetic outcome and the prevention of complications [31]. Nevertheless, introduction of propranolol after the proliferative phase, and even beyond 1 year of age, seems to be safe and of possible efficacy [32, 33].

Contraindications include cardiogenic shock, second- or third-degree heart block, heart failure not controlled by treatment, recent or ongoing hypoglycemic episodes, bronchospasm, and hypersensitivity to propranolol hydrochloride [23, 34].

Before the introduction of oral propranolol, a careful medical and familial history (including familial history of arrythmia or maternal connective tissue disease) and a complete physical examination should be performed with emphasis on cardiovascular and respiratory systems. Patients with parameters (blood pressure or heart rate) outside the normal range, frequent wheezing/asthma or special findings at the clinical examination or anamnesis should be managed in conjunction with a pediatrician/pediatric cardiologist [23]. A pre-treatment electrocardiogram is not systemically required in those with normal parameters [3, 23].

If possible, Hemangeol® is preferred to propranolol preparation to avoid mis-dosing. It is important to realize that the concentrations of Hemangeol® (4.28 mg/mL), Hemangiol® (3.75 mg/mL, approved by the EMA and commercialized in Europe and Canada), and propranolol preparation (usually 5 mg/mL) are different. Propranolol is usually started at a

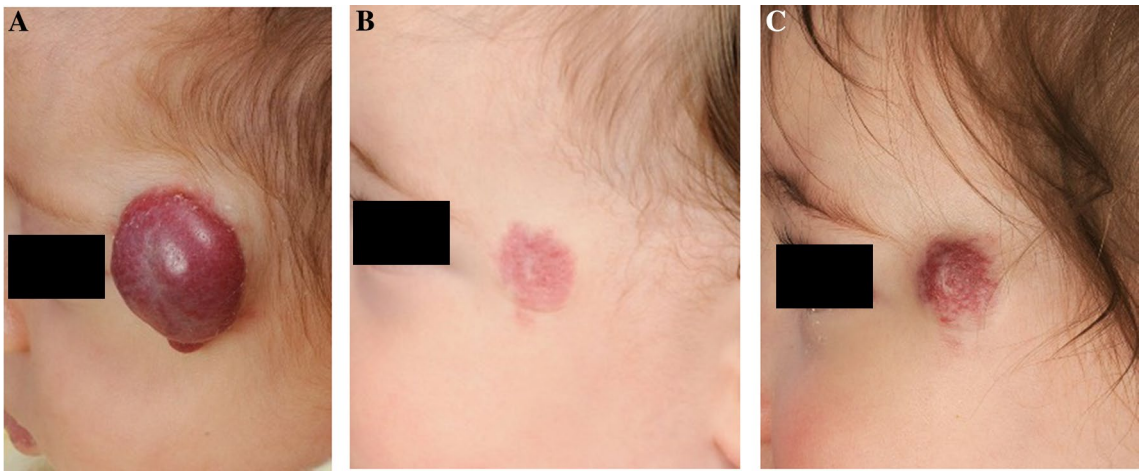

Fig. 7 Rebound after oral propranolol. **A** Infantile hemangioma (IH) at 2.5 months of age; **B** at 12 months, after 10 months of oral propranolol; **C** at 20 months, 10 months after discontinuation of oral propranolol

dose of 1 mg/kg/day divided into two to three doses, with a target dose of 2–3 mg/kg/day, unless there are comorbidities, such as cerebrovascular abnormalities, hyperinsulinism, metabolic or neurological disorders that could justify a lower dosage (typical starting dose of 0.5 mg/kg/day, with individual dosing regimens to be decided by the pediatrician/dermatologist). Specifically, if PHACES syndrome is suspected, an echocardiogram and MRI/MRA of the brain and neck should ideally be performed before the initiation of treatment. If there is no possibility of an MRI/MRA before the initiation, then the starting dose of propranolol should not be over 0.5 mg/kg/day in three doses until the realization of the MRA [23]. However, PHACES syndrome suspicion is not an absolute contraindication to treatment with propranolol, and a multicentric retrospective cohort study reported no serious adverse effects in a population of 76 children with PHACES syndrome treated with propranolol [35].

Initiation in an inpatient (and lower starting dose) setting is advisable for patients <5 weeks of corrected age, and those with cardiovascular or respiratory comorbidities or poor social support. For other patients, an outpatient setting initiation is advisable, with 2-h monitoring after the initial dose and escalation(s) as per on-label recommendations. As more and more experience in initiation of oral propranolol is gathered, and rushed by the COVID crisis, there is now evidence that oral propranolol can be introduced safely at home by caregivers, after obtention of a complete cardiovascular and pulmonary history and a recent complete physical examination by the primary caregiver or pediatrician. A retrospective study of 783 patients demonstrated that in-office monitoring after initial or escalation dose did not detect cardiovascular or non-cardiac events, and that "prolonged cardiovascular monitoring for propranolol initiation and escalation may not be necessary in infants greater that 5 weeks corrected age who have had appropriate pretreatment evaluation and comprehensive patient/guardian education" [36]. The British guidelines for oral propranolol in proliferating hemangioma also recommend an outpatient introduction of therapy without monitoring in patients older than 4 weeks with "no significant comorbidities, born at term, with normal birth weight, established feeds and appropriate weight gain" [23]. Slower escalation could be considered in outpatient initiation without monitoring (with an initial dosage of 0.5 mg/kg/day, gradually increased by steps of 0.5 to 2–3 mg/kg/day) [37].

There is no consensus on the duration of therapy, although 6 months' treatment was superior to 3 months in Léauté-Labrèze's RCT [26], and a phase III study showed that propranolol administered beyond 6 months, up to 12 months of age, increases the success rate in high-risk IH [38]. The dose of propranolol should be adjusted for weight during treatment. Two retrospective studies showed that the risk of rebound (occurring in 12–25% of patients) (Fig. 7) was increased if therapy was discontinued before 12 months of age, in segmental IH, in IH with a deep component, and in females [30, 39]. A recent small retrospective study on 198 patients described that regrowth after oral propranolol treatment was higher in head and neck regions, including subglottic IH. Those localizations could benefit from a higher dosage or a prolonged treatment, and from tapering and carefully monitoring after propranolol discontinuation to detect IH regrowth early and initiate further treatment if necessary [40]. When regrowth occurs, it usually does within 2 months after discontinuation [30]. At the end of treatment, it has been suggested that propranolol should be progressively tapered before stopping to avoid rebound tachycardia and hypertension [41], but this is very controversial, and it is generally admitted that it is safe to stop

propranolol abruptly during or at the end of therapy [23]. However, tapering propranolol could also result in a lower risk of rebound growth [39].

Common side effects are sleep alteration, acrocyanosis and cold extremities, gastrointestinal disturbance, and more rarely asymptomatic transient hypotension or bradycardia, bronchospasm, or bronchiolitis [3, 36]. More severe but rare adverse events (AEs) have been observed, such as symptomatic hypotension, hypoglycemia, and bradycardia. Severe AEs tend to present after prolonged treatment (not at initiation), and in association with a concomitant illness or stressor [36]. Exceptional cases of propranolol-induced hyperkalemia in patients with large or ulcerated IH have been reported [42–45], and β1-blockers (see Sect. 5.1.2) could be an alternative treatment for those rare cases [42]. To minimize the risk of AEs, it is important to educate parents to discontinue the treatment if the patient has a period of fasting and/or vomiting, wheezing, or severe illness. Having a resource person easily reachable is also advisable. Hypoglycemia manifests initially with sweating, tachycardia, shakiness, and anxious appearance, while later manifestations include lethargy, poor feeding, apnea, seizures, stupor, and loss of consciousness. Concerning the impact on sleep, sleep disturbance including insomnia, agitation, or nightmares has been described as the most common side effect (in 2–18.5% of patients [3, 34, 46–50]) and can necessitate a decrease of the dosage, or even cessation of treatment [46]. In a recent prospective study, propranolol did not significantly impair sleep quality and pattern, and most parents considered the impact on sleep as a minor problem [51].

Propranolol has the ability to cross the blood–brain barrier (BBB) and theoretical concerns about adverse effects on neurologic development have been raised. In the large prospective randomized trial conducted by Léauté-Labrèze et al. [26] no neurodevelopmental differences were detected between the propranolol and the placebo group at week 96. Other studies have showed contradictory results, some of them reporting a negative impact of oral propranolol on gross motor development [52, 53], but more recent studies are reassuring [54–57].

5.1.2 Other β-Blockers

Given the concerns about the passage of propranolol through the BBB and the subsequent sleep disturbance or long-term brain development, and given the respiratory side effects, other β-blockers have been introduced in the treatment of IH. The most commonly used molecules are atenolol and nadolol.

Atenolol is a hydrophilic cardioselective (β1) β-blocker that has limited use in pediatric patients [58]. It is the most extensively studied alternative to propranolol, and has a theoretical inability to penetrate the BBB (thanks to its hydrophilic properties) and a reduced risk of hypoglycemia and bronchial hyperactivity (which are due to β2-blockade) [59]. Raphaël et al. first published in 2011 two cases of patients that had to discontinue oral propranolol due to AEs (one with bronchospasm and hypotension, the other with severe sleep disturbance) and were switched to oral atenolol with good tolerance and efficacy [60]. Comparative studies also showed the efficacy of atenolol, but with contradictory results in terms of AEs. However, a tendency to resolution of the sleep disturbance induced by propranolol when switched to atenolol is noted [58, 61]. Recommended dosing was 0.25–0.5 mg/kg/day at initiation, increased up to 2 mg/kg/day, in a single daily dose [62–69]. A recent RCT by Ji et al. [69] showed that propranolol (2 mg/kg/day) and atenolol (1 mg/kg/day) had similar efficacy, with less AEs in patients treated with atenolol, but no difference in severe AEs. Of note, atenolol seemed to work a little bit more slowly than propranolol. Even if propranolol is able to cross the BBB due to its lipophilic characteristics, other β-blockers with hydrophilic properties (such as nadolol or atenolol) could also modulate the activity of neuronal cells and induce central toxicity despite the absence of passage through the BBB by modulating the release of nitric oxide and/or hydrogen peroxide in the hypothalamus. This explains the occurrence of sleep disturbance (even if less frequent) with β1-selective β-blockers [70]. Another advantage of atenolol is its long half-life (6–8 hours), which allows a once-daily treatment [69].

Nadolol is a nonselective hydrophilic β-blocker that also has a theoretical inability to cross the BBB. A first utilization of nadolol was reported in 2013 by Pope et al. [71] with an excellent benefit in patients with proliferating IH. In a small retrospective study, seven patients that had to discontinue propranolol because of sleep disturbance were improved by the switch to nadolol without compromising efficacy [49]. A case of death associated with nadolol for IH has been reported in a 17-week-old girl on 7 weeks of nadolol. The patient had no bowel movement for 10 days before her death, which probably led to accumulation and enterohepatic recirculation of nadolol, as the feces are the primary route of elimination [72].

5.1.3 Corticosteroids

Before the era of propranolol, corticosteroids were the first-line therapy for complicated IH [73]. Corticosteroids retain this indication in the case of contraindications, intolerable AEs, or inadequate response to propranolol [3], or if a rapid response is needed (see below). The optimal dosing of systemic steroids remains unclear and dose ranges most reported in the literature are between 2 and 5 mg/kg/day of prednisone or prednisolone, with 2–3 mg/kg/day considered as optimal [74]. Typical protocols include a full-dose

treatment for 4–12 months followed by progressive tapering for a total treatment of 9–12 months [3]. IH response associated with oral corticosteroids is 43–84.5% [74, 75]. The AEs are frequent and severe: cushingoid appearance, infection, growth retardation, hypertension, mood changes, and osteoporosis [3, 74], with a risk of hypertension and adrenal insufficiency in prolonged use. It has been suggested that a combined therapy of propranolol and a short steroid course (prednisolone 2 mg/kg/day for the initial 2 weeks) is useful when rapid response is warranted (in life- or function-threatening IH, involving the airways or the eyelids, and ulcerated IH) [76].

Corticosteroids can also be delivered as intralesional triamcinolone or betamethasone injections, with clearance rate up to 66.4% [74, 75], but significant AEs are possible; bleeding, infection, cutaneous atrophy, pigmentary changes, cushingoid facies, and growth retardation can result [77]. This can be an option for small IH of the lip or the nasal tip or has been reported for residual IH after treatment with propranolol [78].

5.1.4 Other Systemic Treatments

There are anecdotal reports of response of refractory IH to sirolimus [79]. Interferon and vincristine have been used in severe life- or function-threatening cases, or with severe esthetic prognosis, mainly before the era of propranolol [80, 81]. They should now be abandoned as treatment for IH due to their serious side effects and the efficacy of propranolol [2].

5.2 Topical Treatment

5.2.1 Topical Timolol

Timolol is a nonselective β-blocker similar to propranolol available in a topical gel or liquid formulation for treatment of glaucoma. The first report of six patients with uncomplicated IH in the head and neck by Pope and Chakkittakandiyil [82] has been followed by multiple studies showing good results in terms of efficacy and safety, including a RCT [83–88]. However, a more recent RCT failed to demonstrate true benefit in lesion resolution of early proliferative IH [89]. It has been proved that there is a systemic absorption of timolol when locally applied on IH, and the blood levels of timolol are directly proportional to the doses used [90]. Absorption was higher in thicker IH, and in IH of the scalp [90, 91]. Gel-forming solution is to be preferred as it allows less systemic absorption [92, 93] and is somewhat easier to apply. It also should be noted that timolol is more potent than propranolol, and that by local application, it misses the first-pass liver metabolism that occurs with other β-blockers [3, 94]. It has been suggested that the maximum safe dosing of timolol 0.5% gel-forming solution is one drop per kilogram of bodyweight [95]. On the other hand, Drolet et al. [91] recommended not to exceed two drops a day and to use the same precautions with topical timolol as with oral propranolol: discontinue treatment in case of fasting, bronchospasm, or severe illness. Some have also suggested to use topical timolol as an adjunct therapy to propranolol (propranolol followed by timolol) to shorten the oral propranolol therapy [96, 97]. Given the uncertainty on the amount of systemic absorption of timolol and the good tolerance and safety evidence on propranolol, this is controversial. Concomitant use of timolol and systemic propranolol might cause additive and unpredictable effects, and is not recommended [87]. Topical timolol is a reasonable alternative for the early treatment of small (<2 cm), superficial, thin IH.

5.2.2 Other Topical Treatments

Topical imiquimod has a certain efficacy in reducing IH, but its efficacy is not superior to that of timolol, and it has more side effects (mainly local, with irritation, ulceration, and scarring) [86, 98].

Intralesional bleomycin has been used in intralesional therapy. However, it's efficacy has been shown inferior to propranolol [99] and there a risk of toxicity.

Intralesional bevacizumab [100, 101], which is an anti-VEFG-A, could become an additional option for adjuvant treatment of IH, but has failed to demonstrate an efficacy superior to intralesional steroids [101].

5.3 Laser

Pulsed dye laser (PDL) is the most commonly studied laser for the treatment of IH, and is generally found to be more effective than other types of laser for cutaneous lesions [102]. PDL is considered the first choice for treating residual telangiectasias of IH. It may also be somewhat effective for fatty-fibrous deposits and correction of anatomical distortion, due to the thermo-induced lysis of collagen that promotes the remodeling of the tissue [103]. Laser therapy can also play a part in the treatment of ulcerated IH (see Sect. 5.6). PDL treatment of residual IH can improve esthetical sequelae. Combination of PDL with propranolol has been suggested to represent the most effective way to reduce the healing time and reduce residual lesions [103]. In practice, β-blockers have such an efficacy that it is rarely necessary to combine them with PDL initially.

5.4 Surgery

The need for surgery has significantly decreased since the advent of propranolol. Surgery is usually limited to residual changes and is usually not performed in infancy. There is no

Table 3 Management of ulcerated IH

Intervention	Means of intervention
Local wound care	Atraumatic non-adhesive dressing Barrier creams (zinc oxide) PDL on the bed of ulceration Autolytic debridement
Pain management	Systemic analgesics (acetaminophen) Anesthetic cream (lidocaine or prilocaine-lidocaine cream)
Reduction of the proliferation phase	Systemic β-blockers (propranolol: consider dosage < 1 mg/kg/day) Avoid topical β-blockers (timolol)
Management of infection	Topical antibiotics Systemic antibiotics

IH Infantile hemangioma, *PDL* pulsed dye laser

urgency to intervene as long-term memory and self-esteem are not established until later in childhood [3]. It is reasonable to defer surgery until the age of 3–5 years, but there is no advantage to wait longer as the great majority of IH have reached their maximal involution by the age of 4 years [11]. Early surgery can be considered in ulcerated or bleeding IH recalcitrant to therapy, if there is an obstruction or deformation of vital structures, or if the lesion is localized in an anatomically favorable area and likely to require resection in the future [3].

5.5 Embolization

Embolization is rarely indicated and is restricted to life-threatening IH that have failed to respond to medical management such as hepatic lesions causing severe congestive heart failure and exceptional cases of severe bleeding.

5.6 Treatment of Ulcerated IH

Treatment of ulcerated IH include four major aspects: local wound care, reduction of pain, reduction of proliferation, and management of infection (Table 3). Local wound care has to be adapted to the type of wound, but barrier creams (such as creams containing zinc oxide) or atraumatic non-adhesive dressing are important in all ulcerated IH to reduce pain and improve healing [104]. The use of PDL on the bed of the ulceration (if there is no crust) seems to be useful to accelerate healing [104]. Propranolol is again central in the treatment of ulcerated IH by reducing the proliferation. However, it has been suggested that β-blocker therapy can induce or precipitate ulceration [105]. A recent retrospective study could not establish a cause–effect relationship but suggested that control of the proliferation phase does not always prevent ulceration, and that doses of propranolol > 1 mg/kg/day resulted in longer healing times. They concluded that in ulcerated IH requiring systemic therapy, a lower dosage of propranolol (≤ 1 mg/kg/day) should be considered [19]. We also recommend considering a lower dosage of propranolol in case of IH with a high risk of ulceration since those are often superficial segmental IH that usually respond well to a lower dosage. Topical timolol is not recommended because of the increased risk of systemic absorption and potential toxicity. The rate of infection is high in ulcerated IH. Topical antibiotics are used in the majority of cases, and systemic antibiotics may be required in more severe cases [104, 106].

6 Conclusion

IH is the most common vascular tumor in infancy. Early recognition and management are essential. Associations and complications are important to anticipate so proper early treatment can be initiated. The IHReS is a good tool in general practice to determine when to refer the patient and who requires treatment. Propranolol is the first-line therapy and can bring total resolution in the majority of cases. This has revolutionized our approach to IH treatment. Other β-blockers seem promising when propranolol cannot be used. Counseling of caregivers is essential in the management.

Declarations

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