

An Evaluation of Infantile Haemangiomas: Clinical Presentation, Complications, and Distinct Approaches of Therapy and Management

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Congenital vascular malformations can present in various ways. They may appear as a simple vascular spot in some cases, while in others, they can grow symptomatically, leading to significant disfigurement and potentially life-threatening conditions. Infantile hemangioma is a notable medical issue in childhood that necessitates a thorough approach to diagnosis and treatment. This comprehensive review provides the most recent information regarding the pathogenesis, clinical characteristics, diagnosis, and management of infantile hemangiomas. The literature search was conducted using databases such as PubMed, Web of Science, and Scopus databases as well as clinical trials repositories. The selection criteria included peer-reviewed articles, meta-analyses, relevant book chapters, and clinical studies published over the last 15 years (2011–2026). The search strategy incorporated various keywords, including “infantile hemangioma,” “tumor,” “infant,” “clinical aspects,” “treatment,” “pediatric,” and “children.” Inclusion criteria encompassed studies that diagnosed cutaneous infantile hemangiomas, those requiring treatment, or cases of infantile hemangiomas that were untreated at the time of enrollment and could tolerate imaging procedures. Exclusion criteria included the absence of a normal site for study control, the presence of other vascular abnormalities, inability to tolerate imaging procedures, non-peer-reviewed articles, conference abstracts, and studies lacking sufficient methodological details.

Keywords: Children; Clinical aspects; Infantile haemangioma; Treatment; Vascular anomaly; Vascular tumor.

Infantile haemangioma is the most common type of vascular tumor found in children. Infantile hemangioma (IH) is the most common benign vascular tumor in children, characterized

by a unique life cycle: rapid postnatal proliferation during the first months of life, followed by slow spontaneous involution that can last several years. At the molecular level, IE differs from

other vascular anomalies by the obligatory expression of the GLUT-1 marker (glucose transporter type 1), which histologically identifies the tumor endothelium. Although most IG are clinically uncomplicated, their location in internal organs (particularly the liver) or a large area of involvement can lead to serious systemic disorders, such as high-output heart failure or consumptive hypothyroidism.^{1,2}

According to ISSVA (International Society for the Study of Vascular Anomalies) classification, 2018, all vascular anomalies are divided into basic two groups: vascular tumors and vascular malformations, which are fundamentally different not only by their pathophysiological and structural features, but also according to the clinical signs¹. This places a specific role on the importance in the division of these groups to choose the correct treatment and care.² A clear distinction should be made between vascular tumors (such as infantile haemangioma), which are characterized by cellular proliferation, and vascular malformations (venous, lymphatic, etc.), which are structural defects of blood vessels without signs of active proliferation. For infantile haemangioma sometimes are used such terms as “juvenile haemangioma”, “capillary haemangioma”, “strawberry birthmark”, “strawberry haemangioma”, or “strawberry nevus”.

The dichotomous split into vascular tumours and vascular malformations was initially put forward in 1982, and this fundamental idea is retained in contemporary classification. Alongside that, understanding of vascular anomalies has notably advanced through subsequent decades.^{3,4} Genetic susceptibility sites for many of these were established, novel nosological entities were outlined, sundry pathogenesis mechanisms were uncovered, and fresh treatment modalities were put into practice. In previous works, for example, it was posited that the main pathogenic origins of lymphatic malformations were issues in the embryological progress of lymphatic vessels with subsequent lack of lymphatic conduits and venous vessel connections. In more recent publications, justifications are offered that lymphatic malformations are not outcomes of vasculogenesis flaws but stem from random genetic deviations in specific cells which will enable targeted therapy.⁵

They are also part of LUMBAR association syndrome and PHACE(S) association/syndrome.⁶ Risk factors include anemia in pregnancy, preterm premature rupture of membranes, threatened miscarriage, placenta previa, abnormal amniotic fluid volume, premature rupture of membranes, prematurity, multiple gestations, low birth weight, female sex, progesterone therapy, Caucasian heritage, and family and miscarriage history.^{7,8}

Infantile haemangioma (IH) is the most common benign vascular tumor in children, occurring in 4–5% of infants, with a significantly higher incidence among premature infants and girls. Unlike vascular malformations, which are present at birth and grow in proportion to the child's development, IH has a unique biological cycle consisting of three phases: intensive proliferation (usually in the first 6–9 months), stabilization (plateau), and gradual spontaneous involution, which can last up to 5–10 years. A pathognomonic feature of hemangiomas is the immunohistochemical expression of the glucose transporter GLUT-1, which is normally found only in the endothelium of blood vessels with a barrier function (e.g., the blood-brain barrier or the placenta). Although most hemangiomas are cutaneous and do not require aggressive intervention, visceral forms - particularly liver hemangiomas - pose a significant clinical challenge. Depending on their size and location, they can cause serious systemic complications: ranging from high-output heart failure due to arteriovenous shunting to rare but dangerous tuberculous hypothyroidism caused by the tumor's enzymatic activity.²

Haemangioma is benign tumor that develop from blood vessels. They are characterized by rapid growth, particularly during the first years of life, followed by gradual regression.^{9, 10} These neoplasms may be located on the external skin surface or within internal organs.

Haemangiomas are classified as cavernous or capillary, which depends on the type of blood vessels from which they arise.¹¹ As the revised ISSVA classification of vascular anomalies (2018), kaposiform hemangioendothelioma denote local assertive or borderline neoplasms, distinguished by indications of malignant intrusive burgeoning yet possessing no spread to other sites. In the newborn stage of existence kaposiform

hemangioendothelioma might be wrongly identified as infantile or congenital haemangioma, nevertheless, kaposiform hemangioendothelioma relates to a more forceful clinical progression and poorer outlook.^{12, 13}

In cases where haemangiomas cause severe symptoms or complications, consultation with a specialist, such as a dermatologist, surgeon, or oncologist, is recommended. Careful monitoring of changes in size, shape, or symptoms is essential for timely detection of potential complications and selection of optimal treatment.

This study aimed to conduct a systematic review and analysis of the literature available in PubMed, Web of Science, and Scopus databases as well as clinical trials repositories regarding haemangiomas and to present the findings in a scientific publication.

MATERIALS AND METHODS

The literature search was performed using clinical trials, databases of WHO, PubMed, Web of Science and Scopus databases. The selection criteria included clinical studies, peer-reviewed articles, metaanalyses, and relevant book chapters published over the last 15 years (2011–2026). The search strategy involved using keywords such as vascular anomalies, infantile haemangioma, tumor, infant, children.

Among the inclusion criteria were studies that (1) diagnosis of a cutaneous infantile haemangioma (2) diagnosis of haemangioma requiring treatment (treatment includes: propranolol or topical timolol) or diagnosis of an infantile haemangioma that will not be treated at the time of enrollment (3) able to tolerate imaging procedures (4) were published in English. Among the exclusion criteria were (1) no available normal site for study control (2) other vascular anomaly (3) not able to tolerate imaging procedures (4) non-peer-reviewed articles, editorials, and conference abstracts, as well as (6) studies with insufficient methodological details.

RESULTS

An analysis of clinical cases demonstrated a clear correlation between the morphological type of vascular lesion and the severity of systemic manifestations. In a study of a group of patients with confirmed infantile hepatic hemangiomas, it was noted that focal lesions remained asymptomatic in 92% of cases, whereas diffuse forms were invariably accompanied by signs of heart failure or endocrine dysfunction. Laboratory monitoring revealed a critical decrease in free T4 levels against a background of compensatory TSH elevation in infants with a total tumor volume exceeding [specify value] cm³, confirming the metabolic load threshold at which D3 activity exceeds the



Fig. 1. The Multifaceted Nature of Haemangiomas

Table 1. Examples of completed clinical trials regarding Infantile Haemangioma (clinicaltrials.gov)

Clinical Trials.gov ID	Official Title	Location	Condition	Study type	Intervention / Treatment	Subjects
NCT02061735 ¹⁷	Ontogeny of Infantile Haemangiomas with Skin Imaging Modalities	Cincinnati, Ohio, United States	Infantile Haemangiomas	Observational	Oral propranolol, topical timolol and untreated (observation)	118
NCT00601016 ¹⁸	A Phase II Study of Imiquimod 5 % Cream for the Treatment of Haemangioma in Infancy	Montreal, Quebec, Canada	Haemangioma, Capillary	Interventional, Phase 2	Drug: cream Imiquimod 5% from 3 to 7 times per week; maximum of 4 months	18 infants
NCT06677853 ¹⁹	Timolol Maleate Gel for the Treatment of Infantile Haemangioma	Shanghai, Shanghai Municipality, China	Infantile Haemangioma	Phase 3	Drug: Timolol Maleate Gel and PlaceboDrug: Timolol Maleate GelDrug: Placebo3 times a day (in the morning, noon, in the evening) for 24 weeks	168
NCT04105517 ²⁰	Hemangioli, Post Marketing Surveillance Study (postHemangioli)	Montpellier, France	Infantile Haemangioma	Observational	Hemangioli's dose: 1, 2, 3 or 4 mg / kg / per day in 2 doses	500 Infantsaged 0 to 1 years
NCT01685398 ²¹	Topical Timolol for Superficial Infantile Haemangioma	Bangkoknoi, Bangkok, Thailand	Haemangioma	Interventional, Phase 3	Drug: eye drop 0.5% timolol maleate Drug: Normal salineTopical timolol for 6 months; 4 times per day; application of 1-2 drops of timolol solution on the lesion	48
NCT02731287 ²²	Topical Timolol for Infantile Haemangioma in Early Proliferative Phase	Barselona, Spain	Haemangioma	Interventional, Phase 2	Drug: TimololDrug: Placebotopical 0.5% timolol 2 times per day for 24 weeks	70
NCT01211080 ²³	Off Label Use of Propranolol for Infancy Haemangiomas (PIHS)	Hannover, Germany Hanover, Lower Saxony, GermanyHildesheim,	Haemangioma	Observational	Drug: PropranololTreatment was started at 1mg/kg/day and increased after 24 hours	72 infants

NCT00433940 ²⁴	Immune Suppression of Infants Treated with Steroids	Lower Saxony, Germany Milwaukee, Wisconsin, United States	Haemangioma	Observational	Drug: Prednisolone Evaluation will occur 12 weeks after discontinuing the steroid for its long-term effects on the immune system	16 infants
NCT01072045 ²⁵	Comparative Study of the Use of Beta Blocker and Oral Corticosteroid in the Treatment of Infantile Haemangioma	São Paulo, São Paulo, Brazil	Haemangioma	Interventional, Phase 2	Drug: Propranolol Drug: Prednisone	50
NCT02145884 ²⁶	Topical Timolol Gel for the Treatment of Infantile Haemangiomas	San Diego, California, United States	Haemangioma	Interventional, Phase 2	Drug: timolol maleate 0.5% gelto place 1 to 2 drops twice a day in the center of the haemangioma	26
NCT01010308 ²⁷	Nadolol for Proliferating Infantile Haemangiomas	Toronto, Ontario, Canada	Infantile Haemangioma	Interventional, Phase 2	Drug: Nadolol	20 infants

functional reserves of the thyroid gland. At the same time, dynamic monitoring during propranolol therapy showed an initial decrease in signal intensity on Doppler mapping as early as the second week of treatment, preceding visible regression of the neoplasm's size.^{10, 12}

It typically exhibits swift expansion in bulk with certain steadiness over duration but solely without full fading even following treatment. The pairing of kaposiform hemangioendothelioma and Kasabach-Merritt occurrence in recent infants constitutes a peril to existence grouping (Fig. 1). It is important to differentiate between vascular neoplasms: the so-called Kasabach-Merritt phenomenon (severe thrombocytopenia and consumption coagulopathy) is a specific complication of Kaposi's hemangioendothelioma (KHE) or plexiform angioma. This phenomenon is not characteristic of common infantile haemangiomas, despite their potentially large size, which is a key point for avoiding clinical confusion when establishing a diagnosis.

The occurrence bearing the designations of the originators who initially noted it in 1940 and is defined by adepleting coagulopathy (diminished fibrinogen measure and raised fibrin breakdown products), and marked thrombocytopenia observed as a consequence of platelet entrapment within the lesion.¹⁴ Despite the considerable illness and death occurrence, there exist no evidence-supported standard diagnostic and curing procedures.

Treatment of haemangiomas includes a wide range of approaches, from observation and expectant management to active intervention (Table 1). The decision to initiate therapy may be determined by the size, location, and pathogenesis of the haemangioma. Pharmacological therapy, laser therapy, surgical excision, interventional radiology, and cryomedicine represent some of the available treatment options.^{10, 15, 16}

Haemangioma is a soft tissue tumour of vascular origin. This type of tumour most commonly occurs in children, predominantly localised to the skin.²⁸ A characteristic feature of haemangiomas is their relatively rapid growth, particularly during the first months of life. In most cases, haemangiomas are present at birth, while less commonly they develop during the first months of life. Typically, the tumour affects the skin and

soft tissues; however, various organs may also be involved.²⁹

DISCUSSION

Infantile haemangiomas are a subtype of haemangiomas that arise during the first months

of life and typically grow during the first six months, after which they may gradually decrease in size over several years.³⁰ These haemangiomas are usually bright red or purple in colour and may be raised or flat. They are most commonly located on the face, head, neck, or trunk. Infantile haemangiomas are considered benign and often

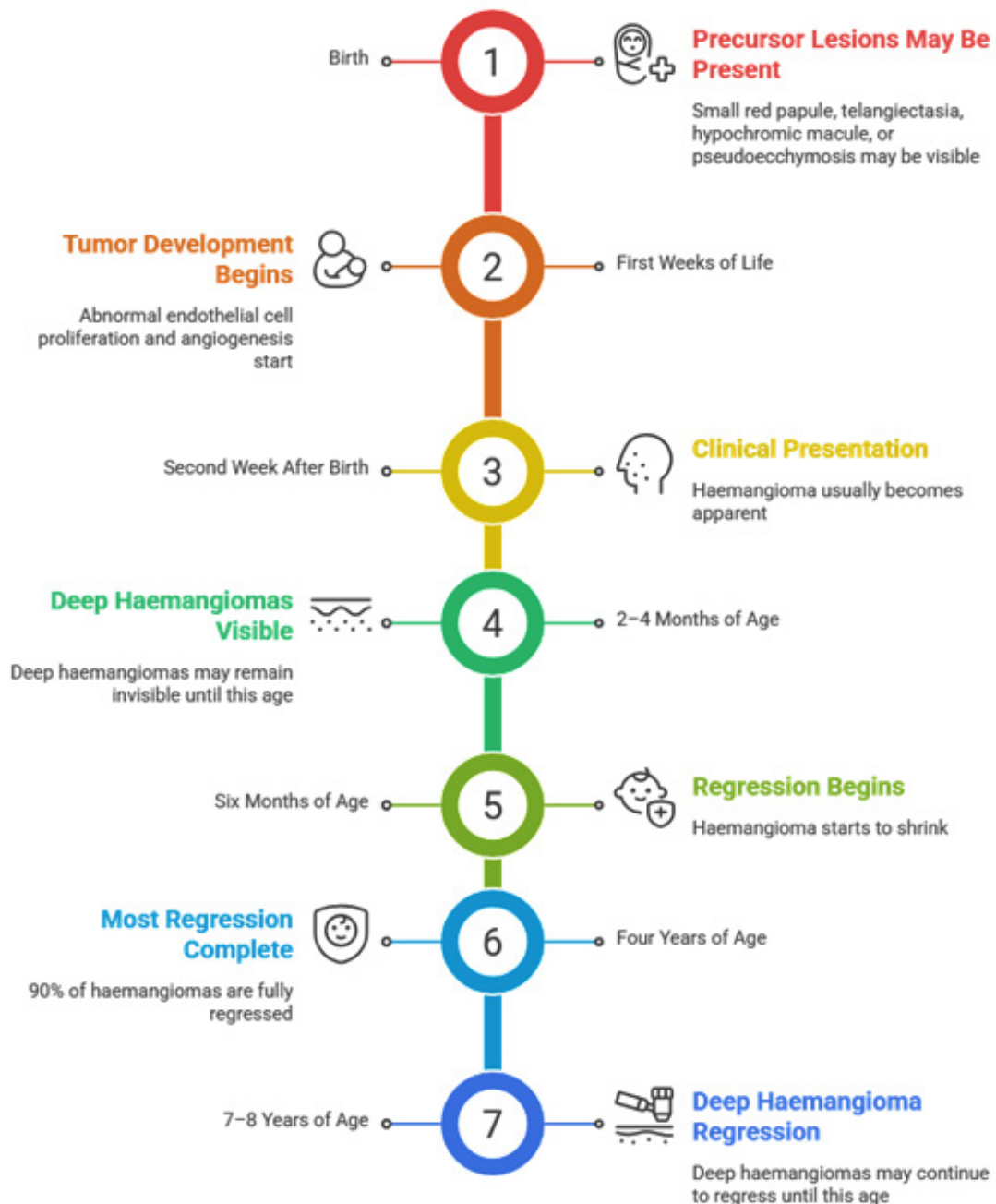


Fig. 2. Infantile Haemangioma Development and Regression Timeline

do not require active treatment, as they frequently resolve spontaneously during the early years of life. However, in certain cases – particularly when the haemangioma is large or located in critical anatomical regions – medical intervention may be required.³¹

Treatment generally begins with an observation-and-waiting strategy, as many haemangiomas resolve spontaneously.

Nevertheless, in some cases, especially when lesions are large or dangerously located, active treatment may be necessary. Large or internal haemangiomas may pose health risks, particularly if they compress surrounding organs or structures. Diagnosis of haemangiomas is typically based on clinical features and imaging studies such as ultrasonography, computed tomography, or magnetic resonance imaging. Accurate assessment

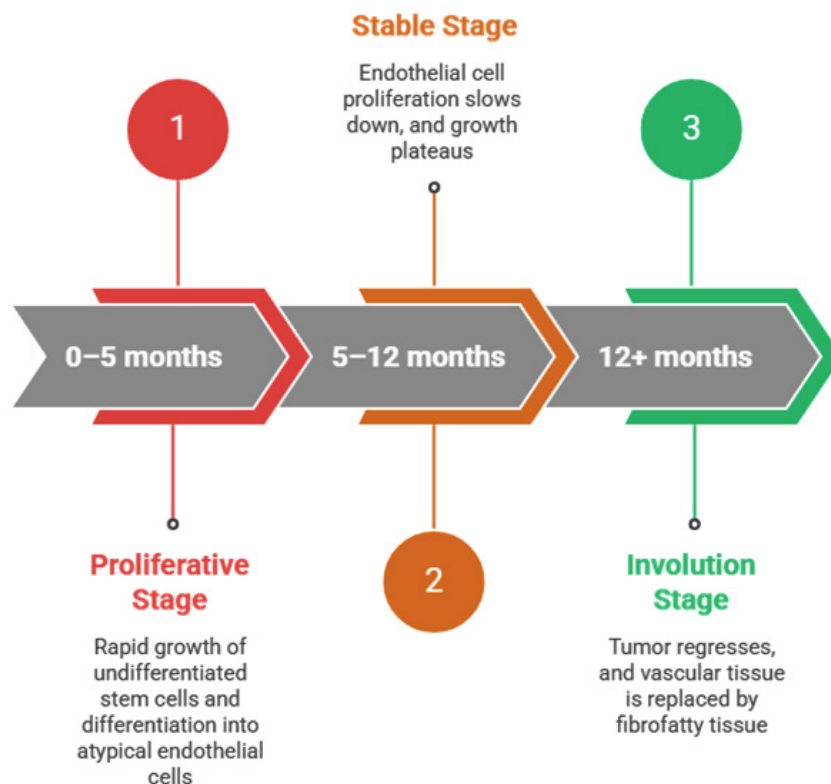


Fig. 3. Stages of Infantile Haemangioma Development

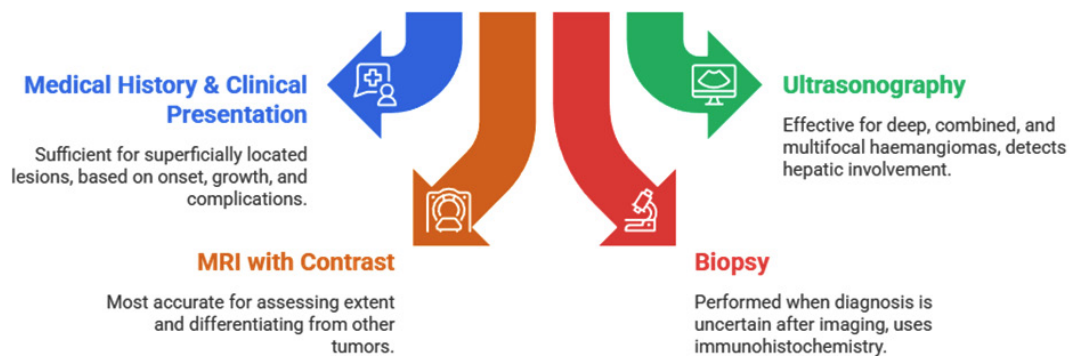


Fig. 4. The Diagnostic of Infantile Haemangioma

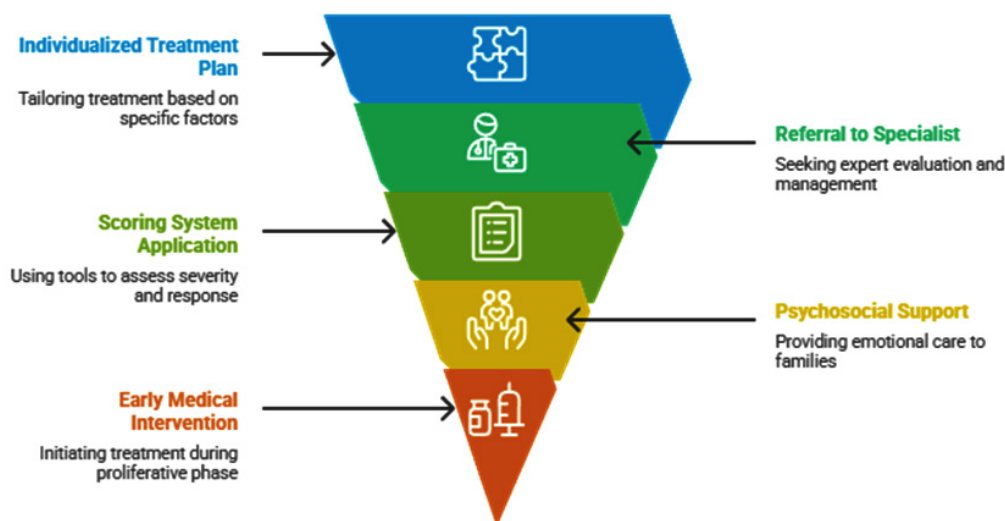


Fig. 5. The main stages of infantile haemangioma treatment

of haemangioma size and characteristics assists in determining the most appropriate treatment strategy.³²

These advances contribute to improved diagnostic and therapeutic approaches, reducing the risk of complications and enhancing patient prognosis. However, further research and clinical trials are required to translate these findings into routine clinical practice.³³

Haemangioma is a benign soft tissue tumor of vascular origin. The pathogenesis of infantile haemangiomas is not studied yet. Such pathology is caused by abnormal activation of blood vessels endothelial cells, which leads to the local clonal expansion. Haemangiomas are understood to be clonal expansions of cells derived from embolized placental cells or bone marrow cells. This idea aligns with the observation that the expression patterns of cellular markers - such as GLUT-1, merosin, FcR2, Lewis Y antigen, type 3 iodothyronine deiodinase, indoleamine 2,3-dioxygenase, and IGF2 - as well as the transcriptomes in infantile haemangioma tissue, closely resemble those found in endothelial cells (ECs) of fetal microvessels in the human placenta.³⁴ This metabolic change, caused by hypoxia and increased GLUT-1 expression, activates HIF-1 α stabilization in endothelial cells, which triggers angiogenic signaling pathways (including VEGF) to adapt the vascular network to low oxygen levels.

Furthermore, Strub *et al.* identified that the chromosome 19 miRNA cluster (C19MC), known for its expression in the placenta, is also expressed in infantile haemangioma ECs. Elevated levels of circulating C19MC miRNA have been detected exclusively in patients with infantile haemangiomas, with concentrations correlating to tumor size and responsiveness to oral propranolol treatment. This discovery has positioned C19MC miRNA as a promising potential biomarker for infantile haemangiomas. Additionally, various studies indicate that hypoxia - whether occurring in utero or locally - may act as a key trigger for haemangioma development. The proliferative phase of haemangiomas is thought to represent the body's compensatory response to restore oxygen levels in hypoxic tissue.^{35,36}

Infantile haemangiomas (IHs) often present with precursor lesions marked by localized pallor, dilated capillaries, and dark red patches. GLUT-1 has been identified as a critical sensor in hypoxia signaling, playing a role in IH formation.³⁷ Beyond hypoxia, research indicates that the renin-angiotensin system (RAS) contributes to IH development through the vasoactive peptide angiotensin II (ATII). This system acts as a significant regulator of hemogenic endothelium, primarily via VEGF signaling and osteoprotegerin, a pro-tumor survival factor. These elements collectively help sustain a vasculogenic and anti-

apoptotic environment conducive to IH growth.³⁸

Interestingly, serum renin levels in infancy and childhood align with the natural progression of IHs. The therapeutic use of α -blockers, which inhibit renin release, has proven effective in accelerating the regression of these tumors.^{10, 39} Additionally, elevated estrogen levels during pregnancy may influence fetal vascularization and promote atypical vascular proliferation. Of particular importance is 17 β -estradiol, which is thought to play a pivotal role in IH development. Tissues affected by IH frequently exhibit unusually high levels of estrogen receptors. Estrogen's impact on angiogenesis appears to involve the upregulation of angiogenic factors like VEGF, ultimately driving abnormal vascular formation and contributing to IH pathology.^{36, 40}

Research has shown that within certain inflammatory environments, inflammatory factors can work in synergy with other cytokines to enhance neovascularization. A significant imbalance in these factors may contribute to the onset of Infantile haemangioma.⁴¹ Additionally, the involvement of specific cell subtypes, such as macrophages, mast cells, pericytes, and telocytes, warrants further investigation, as these cells may play critical roles in regulating the vascular mechanisms underlying the development of Infantile haemangiomas.³⁷

Achieving a comprehensive understanding of these mechanisms could pave the way for more effective targeted therapies. Developing stable and reliable models of Infantile haemangioma would offer a standardized experimental framework to better explore its pathogenesis. As previously mentioned, the progression of Infantile haemangiomas typically occurs in two main phases: the proliferative phase and the involution phase.⁴¹

The condition usually presents within the first few weeks after birth. During the early proliferative phase, the growth of Infantile haemangiomas is at its fastest, typically occurring within the first 3-5 months and peaking between weeks 5 and 8 when lesions often reach up to 80% of their maximum size.⁴² The late proliferative phase follows, marked by much slower growth and typically lasting until the child reaches 9-12 months of age. In exceptional cases, growth may persist beyond 3 years in large, segmental, or deep haemangiomas. The involution phase generally

begins during the first year of life and can continue for 3 to 9 years, eventually leaving fibrofatty residuum in approximately 70% of affected patients.⁴³

Among benign neoplasms of the skin and soft tissues, haemangiomas occur with a frequency of 57%. In 30% of cases, haemangiomas are detected at birth, while in 70% of cases they develop during the first weeks of life.⁴⁴ Approximately 60% of haemangiomas occur on the head and neck; they may also be found on the trunk, extremities, genitalia, and in internal organs such as the liver and intestines.

Vascular anomalies are divided into vascular malformations and vascular tumors. According to the ISSVA classification, vascular tumors are divided into infantile and congenital haemangiomas, tufted haemangiomas, spindle-cell haemangiomas, epithelioid haemangiomas, and pyogenic granulomas (lobular capillary haemangiomas).^{10, 45}

Based on the depth of involvement, haemangiomas are classified as superficial, deep, mixed, reticular, abortive with minimal growth, and others.^{10, 36, 42} Clinically, superficial haemangiomas present as reddish or bright red papules, nodules, or plaques on normal skin. Superficial haemangiomas resemble strawberries and are therefore also referred to as "strawberry haemangiomas" or capillary haemangiomas. They represent the most common type of infantile haemangioma. Deep Haemangioma, also known as cavernous haemangioma, this type presents as an elevated nodule located beneath the skin surface and deforms upon pressure. It is often bluish in color, with or without central areas of telangiectasia, and is relatively rare. Mixed Haemangioma represents a combination of superficial and deep haemangiomas and often appears as a superficial haemangioma overlying a deeper lesion. Mixed haemangiomas may grow rapidly and spread over a large surface area.

Based on anatomical distribution, haemangiomas are classified as focal, multifocal, segmental, or indeterminate. Focal infantile haemangiomas are solitary, isolated lesions with well-defined localization, presumably arising from a single focus. They most commonly present as papules, plaques, or nodules. Multifocal infantile haemangiomas consist of multiple, scattered

lesions that do not involve a specific body region and originate from several foci. Segmental infantile haemangiomas often present as plaques or patches arranged linearly or in a geographic pattern with well-defined borders over specific skin regions (upper or lower extremity, half of the face, etc.), usually with a diameter more than 5 cm.

Indeterminate infantile haemangiomas do not belong to any of the above categories, lack clear localization, and may partially or completely proliferate.^{10,43,44}

Infantile haemangioma is the most common vascular tumor of early childhood, affecting approximately 4–10% of infants. This tumor is characterized by abnormal proliferation of endothelial cells and angiogenesis and is not usually present immediately after birth; its development begins during the first weeks of life. In some patients, precursor lesions may be present at birth, such as a small red papule, telangiectasia, a hypochromic macule (corresponding to an anemic nevus), or pseudoecchymosis.^{45,46}

This tumor affects girls more frequently than boys (approximately 3:1), particularly those of European descent, and is more common in premature infants, infants with low birth weight (less than 1000 g), and infants born from multiple pregnancies. Clinical presentation and disease course do not differ between full-term and preterm infants. Infantile haemangiomas most commonly localize to the head and neck (70%), chest and trunk (25%), and upper or lower extremities (5%).⁴⁷ Clinically, infantile haemangiomas usually become apparent during the second week after birth; however, deep haemangiomas may remain invisible until 2–4 months of age.⁴⁸

Regression of infantile haemangiomas begins after six months of age (Fig. 2). In 90% of children, regression is complete by the age of four years; however, in deep haemangiomas, regression occurs more slowly and may continue until 7–8 years of age. Approximately 5–10% of infantile haemangiomas are destructive and may result in telangiectasia, ulceration, scarring, or hyperpigmentation.⁴⁹

It has been established that infantile haemangiomas undergo three stages of development (Fig. 3).^{10,44} The first stage (proliferative stage) is characterized by the proliferation of undifferentiated stem/progenitor cells. These cells differentiate into

atypical vascular endothelial cells characteristic of infantile haemangiomas. In most cases, the proliferative stage ends by five months of age. In deep infantile haemangiomas, this stage may last 9–12 months and, in rare cases, up to two years.

The subsequent stage (stable stage) involves a gradual reduction in endothelial cell proliferation, followed by the involution stage, during which the tumor regresses and vascular tissue is replaced by fibrofatty tissue.⁵⁰

Most infantile haemangiomas are uncomplicated and do not require treatment; however, approximately 10% may cause serious complications and require intervention.⁴⁹ Factors contributing to the development of complications include segmental, indeterminate, large haemangiomas, and haemangiomas located on the face. The type of complication depends on the size and location of the lesion. This particularly applies to haemangiomas located in life-threatening areas, those causing functional impairment, those with visceral involvement, or those associated with ulceration.⁵⁰ Life-threatening complications are associated with haemangiomas located in the airway and hepatic haemangiomas. Functional complications arise due to obstruction of vital structures or impairment of organ function. Such complications may be caused by periocular haemangiomas, nasal haemangiomas, lip haemangiomas, parotid haemangiomas, haemangiomas of the auricle, and haemangiomas of the breast.

Local complications primarily result from ulceration, most commonly occurring in cosmetically sensitive areas. Ulceration is the most frequent complication of infantile haemangiomas, with an incidence ranging from 10% to 30%.⁵¹ Ulceration most often occurs between 4 and 8 months of age. It is more common in large haemangiomas and in lesions located on the lower lip, neck, and diaper area (perineal region). An early sign of ulceration is a change in color along the margins of the lesion.

Infantile haemangiomas affecting the airway may lead to life-threatening complications. Symptoms of airway obstruction may occur with or without cutaneous haemangiomas. Skin lesions located in the mandibular region, particularly if bilateral, are markers of high risk for airway involvement. Five anatomical regions have been

identified as high-risk zones: left preauricular area, right preauricular area, chin, lower lip, and anterior neck. Patients with involvement of four or more of these regions had symptomatic airway haemangiomas in 63% of cases.^{46, 48}

Involvement of other organs has also been described. Multiple cutaneous infantile haemangiomas in children have been identified as potential markers of hepatic haemangiomas, and recent data suggest that the presence of five or more cutaneous lesions warrants screening for hepatic involvement.⁵²

Although the development of tuberculous hypothyroidism is traditionally associated with diffuse or large multifocal hepatic haemangiomas, high expression of type 3 iodothyronine deiodinase (D3) is not a feature exclusive to multiple lesions. The critical determinant of systemic metabolic shift is the total active mass of tumor tissue ("tumor burden"), rather than the number of individual lesions. Consequently, even solitary giant haemangiomas with high endothelial proliferative activity are capable of producing sufficient amounts of D3 to cause massive inactivation of thyroxine (T4) and triiodothyronine (T3). This confirms that monitoring thyroid function is advisable for all patients with solid vascular liver tumors, regardless of their morphological configuration, since the intensity of enzymatic hormone degradation directly correlates with the total volume of proliferating endothelium.

Functional Complications. Infantile haemangiomas that cause functional impairment are most commonly located in the periorbital region (12–24% of cases). Periocular infantile haemangiomas, particularly those larger than 1 cm, may exert persistent effects on vision, leading to amblyopia, astigmatism, or strabismus. Mixed and deep haemangiomas may result in ptosis, proptosis, incomplete eyelid closure, and optic nerve involvement.

Depending on their size, haemangiomas of the lip may cause functional impairment or lead to significant cosmetic deformity. Lesions located on the lower lip may interfere with feeding and normal dental development. Infantile haemangiomas affecting the ear may cause cartilage destruction, cosmetic deformity, narrowing of the external auditory canal, hearing impairment, or hearing loss.⁵³ Infantile haemangiomas of the nasal tip

may cause separation of the lower lateral nasal cartilages, resulting in a bulbous nasal deformity. Haemangiomas of the breast, particularly those involving the nipple and areola, may cause functional impairment of the mammary gland and cosmetic defects. Cosmetic defects are primarily caused by scarring of the skin and deformation of specific body regions.

The risk of disfigurement is significantly higher than the risk of functional or life-threatening complications.⁵⁴ Deformities resulting in cosmetic defects may have a negative impact on quality of life, social activity, and the emotional and psychological well-being of the child. Therefore, primary care physicians (district pediatricians and family physicians) should be knowledgeable in the diagnosis of infantile haemangiomas and able to identify children who require referral to subspecialists in order to prevent complications. Early diagnosis and assessment of disease severity are crucial for timely initiation of treatment and reduction of complication risk.

In the presence of superficially located lesions, the diagnosis of infantile haemangioma is usually based on medical history and clinical presentation (Fig. 4). However, deeply located infantile haemangiomas are more difficult to diagnose. When collecting medical history, it is essential to determine the time of lesion onset, growth dynamics, and the presence of complications. In most patients, additional diagnostic investigations are not required; however, in certain cases they may be necessary. Among instrumental diagnostic methods, ultrasonography and magnetic resonance imaging are considered the most effective, non-invasive techniques suitable for differential diagnosis of haemangiomas and other vascular anomalies.^{44, 55}

Ultrasonography is indicated for deep, combined, and multifocal infantile haemangiomas and allows detection of hepatic involvement. On ultrasonography, infantile haemangiomas appear as well-defined lesions with high vascular density and rapid blood flow; during involution, areas of increased echogenicity (fatty replacement) may be observed. Ultrasonography enables assessment of tumor size (volume and diameter) and depth, which is essential for evaluating disease dynamics. Lesion type can usually be determined based on physical examination and Doppler imaging.^{47, 51}

Magnetic resonance imaging with contrast enhancement is considered the most accurate diagnostic tool for infantile haemangiomas, as it demonstrates the extent of involvement and helps differentiate haemangiomas from other tumors. MRI is primarily used to confirm the clinical diagnosis, assess lesion extent, and determine the feasibility of surgical resection.⁴⁸

Biopsy is performed when the diagnosis remains uncertain after imaging studies. Histological examination allows determination of the stage of haemangioma development using tissue-specific immunohistochemical markers (GLUT-1, merosin, Lewis Y antigen, etc.), which aid in differentiating infantile haemangiomas from other vascular tumors and malformations, such as congenital haemangiomas, tufted angiomas, or pyogenic granulomas. These latter entities do not express these antigens.^{56,57}

Morbidity and mortality associated with infantile haemangiomas range from life-threatening complications, such as bleeding and airway obstruction occurring primarily during the proliferative phase, to scarring and disfigurement observed mainly during the involution phase. A hallmark of modern vascular anomaly management is a multidisciplinary approach; therefore, specialized high-level care can be provided only in a multidisciplinary hospital setting. Venous malformations, that are sometimes called “cavernous haemangiomas” or “cavernomas”, can present their first signs in early age, though the peak of clinical presentation appears by the age of 20 years. Less than 10% of extremities. Venous malformations, sometimes referred to as cavernous haemangiomas or cavernomas, can begin to show symptoms in early childhood, but the peak age for clinical presentation typically occurs around 20 years. Fewer than 10% of venous malformations in the extremities are noticeable before adolescence. Based on this, urgent therapy is generally unnecessary for newborns in most cases.

Arteriovenous malformations (AVMs), on the other hand, may present in newborns as a pink or red spot, which is indistinguishable from typical capillary birthmarks. In young children, rapid growth or complications from AVMs are rare, so immediate treatment is likewise not usually required.

Within the first two months of life,

haemangiomas can nearly double in size. During this rapid growth phase, a localized infantile haemangioma covering an area of 4 cm² may expand into a segmental haemangioma spanning 40 cm².^{58,59} This accelerated growth is linked to the proliferation phase of haemangiomas. Hepatic haemangiomas, a type of vascular tumor, can range from mild and asymptomatic to potentially life-threatening. In cases of multifocal and widespread hepatic infantile haemangiomas, the mortality rate is approximately 16%. Most fatal cases involve the extensive form of the condition, often accompanied by abdominal compartment syndrome and heart failure.⁶⁰ These serious complications necessitate prompt and active treatment strategies in early infancy. Infantile haemangiomas are high-flow vascular lesions that may lead to cardiac failure during their growth phase due to increased blood shunting. Additionally, hepatic infantile haemangiomas are associated with acquired consumptive hypothyroidism. This occurs because these haemangiomas produce high levels of type 3 iodothyronine deiodinase, an enzyme that deactivates thyroid hormones. However, this form of hypothyroidism does not occur in congenital haemangiomas, whether hepatic or in other locations.

Congenital haemangiomas are rare vascular swellings, with their exact prevalence remaining unclear as only isolated cases have been described in literature.⁶¹ Notably, no other researchers have yet established CHs as a distinct nosological entity. A study involving nine patients with CHs found them to account for 3.2% of clinical cases. These swellings typically appear around the 12th week of gestation and are often detected via fetal sonography. They reach their maximum size during the final stages of pregnancy and naturally regress during the infant's first months of life. For this reason, continuous monitoring during this period is crucial.

One of the most severe complications of kaposiform hemangioendothelioma involves coagulation disorders leading to thrombocytopenia, a condition known as Kasabach-Merritt syndrome.⁶² When surgical removal of such swellings is possible, the blood-related abnormalities resolve immediately post-surgery. However, radical excision of these lesions is often challenging due to their size and proximity to surrounding tissues.

Heparin has been deemed unsafe based on clinical trials, and the use of platelet concentrates in treating newborns with hemangioendotheliomas has shown adverse effects, such as accelerated swelling growth and significant platelets consumption. In such cases, maintaining platelet levels becomes difficult due to their short half-life post-transfusion. As a result, initiating pharmacologic treatment promptly is critical to managing swelling size and minimizing associated blood complications.⁶³

Despite ongoing research efforts, treatment strategies for vascular anomalies in infants remain distinct from those applied to infantile haemangiomas, with the latest international guidelines providing benchmarks for managing complex cases. While corticosteroids have demonstrated efficacy in correcting thrombocytopenia in newborns, additional treatments are often necessary to achieve comprehensive outcomes. Clinical decisions regarding therapy are generally justified by the severity of complications, which may include airway obstruction leading to respiratory failure in neck or head lesions, liver dysfunction, hypothyroidism, or cardiovascular issues in infants with hepatic involvement.⁴⁸

Selecting an appropriate treatment approach for vascular anomalies requires careful consideration, not only in choosing the optimal intervention but also determining the best time to initiate therapy. Importantly, not all vascular anomalies respond to treatment, nor do they always warrant immediate intervention. In many cases, a cautious approach involving watchful waiting proves more pragmatic than premature therapeutic action without fully understanding the condition's progression. Aggressive procedures like embolization or sclerotherapy may result in significant tissue damage through compromised blood flow or local inflammation, especially when extensive areas are affected. Surgical interventions targeting lymphatic anomalies can pose a risk to vital functions due to their proximity to critical anatomical structures, further underscoring the need for age-appropriate treatment planning.⁶⁴

Thrombocytopenia linked with large femoral haemangiomas accompanied by small red skin lesions was first documented in 1940 by Kasabach and Merritt. Before 1993 - when Zukerberg *et al.* classified kaposiform

hemangioendothelioma as a distinct condition—it was described in medical literature under various terms such as “giant haemangioma/angioma with Kasabach-Merritt phenomenon,” “haemangioma with Kaposi’s sarcoma-like features,” or “Kaposi-like juvenile hemangioendothelioma.” The incidence rate for Kasabach-Merritt syndrome varied widely from 10% to 80%, and correlations were noted between tumor size and patient age. For instance, the syndrome was reported in 79% of infants under one year old, 47% of children aged 1–5 years, 43% of those aged 3–12 years, and only 10% in adolescents and young adults aged 13–21 years. Larger tumor sizes significantly increased the likelihood of Kasabach-Merritt syndrome developing; patients without the syndrome had average tumor sizes of 12cm² compared to an average of 49cm² among those affected.⁶⁵ Conventionally, platelet counts of less than 100 x 10⁹ /L are associated with Kasabach-Merritt syndrome; however, findings from this study revealed platelets never exceeding levels of 20 x 10⁹ /L within affected individuals.⁶⁶

Numerous therapeutic approaches have been outlined for the treatment of kaposiform hemangioendothelioma. Surgical excision of swelling is viable in only 18% of patients. For cases where removal is not an option, a broad spectrum of treatments has been proposed. Techniques such as embolization, sclerotherapy, and radiotherapy are not commonly utilized due to their relatively low success rates, which lie below 30%. Additionally, some of these methods may pose significant risks, particularly for infants.

Treatment guidelines for infantile haemangiomas exhibit minimal variation, underscoring the importance of tailoring therapy to the individual needs of the patient (Figure 5).^{67, 68} Decisions should consider factors such as the lesion’s size, morphology, location, risk or presence of complications, likelihood of scarring or disfigurement, the patient’s age, and the lesion’s growth or involution during evaluation. Infants suspected of having haemangiomas requiring intervention should be promptly referred to a vascular anomaly specialist, ideally by their fifth week of life. Tools like the Infantile Haemangioma Referral Score assist primary care physicians in identifying potential treatment candidates.^{69, 70}

Additional scoring systems, such as

the Haemangioma Severity Scale (used to determine whether treatment is necessary) and the Haemangioma Activity Score (for monitoring therapeutic response), provide reliable assessments of disease burden based on clinical presentations.⁷¹ These models offer standardization in decision-making and serve as valuable tools for research. Equally significant are the psychosocial aspects of care; offering emotional support and guidance to families is critical for ensuring effective management of infantile haemangiomas.⁷²

The overarching goals of treatment include the prevention or reversal of life-threatening or function-threatening complications, minimizing disfigurement caused by residual skin changes, reducing psychosocial distress for both the patient and their family, and adequately addressing ulceration to prevent scarring, bleeding, infection, and pain. Medical treatments are most successful when initiated during the early proliferative phase of haemangioma development- preferably within the first two to three months following birth.⁷³ Below, we discuss the therapeutic advancements available in modern medicine.

A meta-analysis published in 2015 by Liu X et al. (2016) and Yao W et al. (2018) identified vincristine as the most effective treatment for kaposiform hemangioendothelioma.^{74,75} However, more recent studies have shifted focus to mTOR inhibitors, such as sirolimus and everolimus, citing their superior efficacy compared to vincristine.⁷⁶ Despite these promising observations, the available data remain limited, as most studies report only small case series. Furthermore, there is a lack of reliable evidence regarding the safety of these medications in neonates.

Among the reported side effects during mTOR inhibitor treatment are dyslipidemia and immunosuppression. In one case, dyslipidemia prompted treatment discontinuation in a child under the age of one.⁷⁷ Immunosuppression was primarily noted when therapy included prednisone. Notably, two fatal outcomes were officially reported for the first time in 2018. Both cases involved pneumocystis pneumonia that occurred during sirolimus treatment following prednisone administration in young children with kaposiform hemangioendothelioma and Kasabach-Merritt phenomenon.⁷⁸ The patients, aged 1 month and 5 months at the start of treatment,

experienced infectious complications within 2 and 1 months, respectively. Given the reported fatalities caused by *Pneumocystis pneumonia* during sirolimus therapy, strict adherence to safety protocols is mandatory. To minimize the risk of infection in infants, prophylactic treatment with cotrimoxazole (trimethoprim/sulfamethoxazole) is strongly recommended throughout the entire course of mTOR inhibitor therapy. This approach significantly improves the safety of treatment for complex vascular tumors, making sirolimus therapy clinically acceptable even in young patients.

In another study, Czechowicz et al. detailed the outcomes of sirolimus treatment in six neonates with a median age of 14.8 days.⁷⁹ Two of these children were diagnosed with kaposiform hemangioendothelioma. The report highlighted that sirolimus concentrations in the blood were notably higher in these patients after six doses compared to children with lymphatic malformations. Unfortunately, one of the cases resulted in mortality.

Given the mixed outcomes and safety concerns surrounding sirolimus as a treatment for newborns, further research is necessary to establish its efficacy and safety profile in this vulnerable population.

Recent research by Roca et al.³ has highlighted that we are entering an era of molecularly targeted therapy and personalized medicine. In this context, naturally occurring substances show great potential for both tumor treatment and prevention. Plant extracts, in particular, exhibit strong specificity and relevance to cancer therapy. They are generally non-toxic and have few side effects, making them promising candidates for infantile haemangiomas treatment. 15,16-Dihydrotanshinone I, a key bioactive compound of Tanshen (*Salvia miltiorrhiza*), is used in traditional Chinese medicine to treat hematological abnormalities.⁹ It inhibits haemangiomas by inducing pro-apoptotic and anti-angiogenic mechanisms.⁹ Another example is 'Ankaferd Blood Stopper, a natural hemostatic and antimicrobial medicine made from a blend of five different plant extracts (*Urtica dioica*, *Glycyrrhiza glabra*, *Thymus vulgaris*, *Vitis vinifera*, and *Alpinia officinarum*).⁸⁰ Numerous clinical and experimental studies have demonstrated its quick effectiveness

in stopping external repetitive bleeding in case of infantile haemangiomas.^{80,81}

CONCLUSION

This comprehensive review provides the latest insights into the pathogenesis, clinical features, diagnosis, and management of infantile haemangiomas. Advancements in the management of these conditions are likely to stem from enhanced research into their genetic and molecular foundations, aiding the identification of diagnostic markers and a deeper understanding of the influence of various growth factors. Additionally, progress in creating novel pharmacological treatments and techniques, alongside the establishment of standardized protocols for long-term monitoring, will help differentiate cases that necessitate intervention from those suitable for observation. Such developments aim to achieve better outcomes while minimizing side effects.

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