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A Review of Infantile Hemangiomas

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Introduction:

Infantile hemangiomas (IHs), the most prevalent vascular tumors among infants, have garnered considerable attention due to their unique characteristics and clinical challenges. These tumors, initially defined distinctively by Mulliken and Glowacki (1982), emerge postnatally, undergo phases of proliferation and involution, and typically regress over time (1,2). While many IHs resolve without complications, some may lead to impairment of vital functions, scarring, or disfigurement. The complex pathogenesis of IHs remains enigmatic, with various risk factors implicated in their development. Correct diagnosis and appropriate treatment are crucial aspects of managing IHs. This article will review the current literature on the risk factors, pathogenesis, clinical presentation, treatment, and prognosis of IHs.

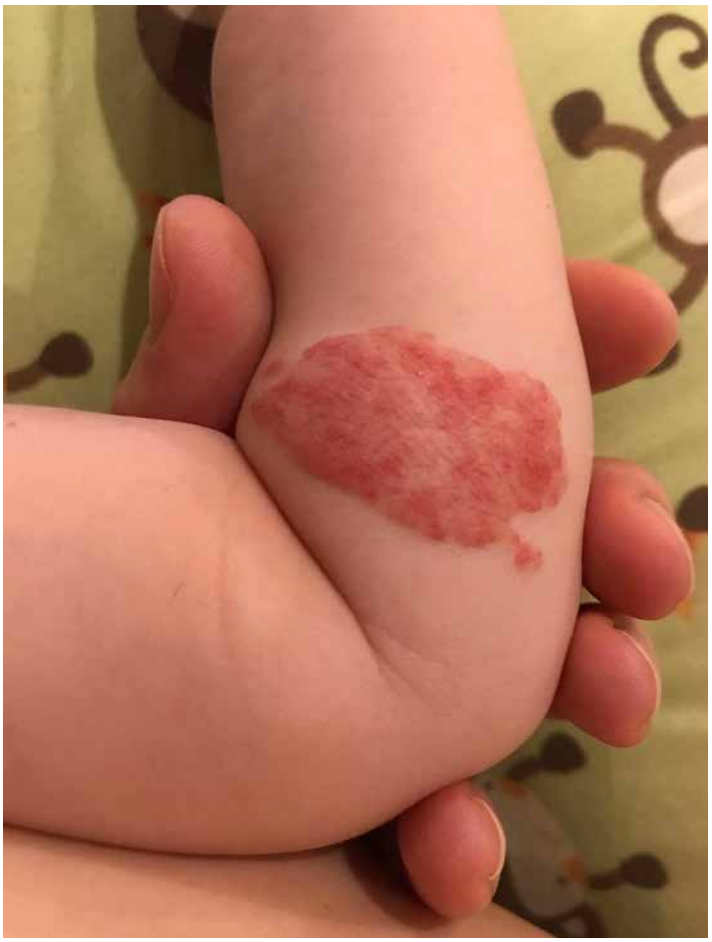

Figure 1. Resolving infantile hemangioma on arm after treatment (17).

"Infantile hemangiomas (IHs) are multifactorial vascular tumors whose etiology involves a combination of genetic predisposition and environmental factors. Female sex has been identified as a consistent risk factor, with IHs occurring more frequently in girls."

Risk Factors:

Infantile hemangiomas (IHs) are multifactorial vascular tumors whose etiology involves a combination of genetic predisposition and environmental factors. Female sex has been identified as a consistent risk factor, with IHs occurring more frequently in girls. Prematurity, low birth weight, and Caucasian ethnicity have also been associated with an increased likelihood of IH development (5). Additionally, there is a higher prevalence of IHs among infants with a family history of these tumors, suggesting a genetic component. Maternal factors such as advanced maternal age and certain pregnancy-related conditions, like preeclampsia, have been explored as potential risk factors, though further research is needed to elucidate their precise contributions (6,7). While these factors offer insights into the complex pathogenesis of IHs, ongoing research is necessary to understand the interplay between genetic susceptibility and environmental influences better.

Pathogenesis:

Infantile hemangiomas (IHs) are infancy's most common benign vascular tumors, characterized by rapid growth during the first few months of life, followed by gradual regression over several years. The pathogenesis of IHs involves complex interactions between genetic, hormonal, and environmental factors (8). Recent studies have highlighted the role of somatic mutations in genes such as GLUT1 (SLC2A1) and KRAS, which contribute to the aberrant endothelial cell proliferation observed in IHs (7,8). These mutations lead to dysregulated angiogenesis, vasculogenesis, and vascular

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Risk severity	Manifestation
Low	IH >2cm on trunk WITHOUT sharp transition to unaffected skin OR <2cm on extremities
Intermediate	IH >2cm on trunk with sharp transition to unaffected skin or rapidly evolving OR focal perineal WITHOUT ulceration

High	Any IH w/ ulceration or if located on:
	• Large (>5cm) truncal or extremity IH
	• Breast
	• Oral mucosa
	• Neck or scalp >2cm (during a growth phase)
	• Face
	  ○ Nasal tip or lip of any size
	  ○ OR if >1cm at <3mo
	  ○ OR >2cm at ≥3mo

Highest	Large or segmental scalp, face, lumbosacral, perineal IH, OR >5 IH with abdominal U/S findings of IH OR any periorbital IH impacting vision, eyelids, or causing ptosis or proptosis

Figure 2. Table adapted from Frieden et al. 2020 outlining the levels of severity with the clinical presentations to determine management (15).

maturation, ultimately forming the hemangioma (9).

Moreover, emerging research has demonstrated the involvement of various signaling pathways, including the Rho/ROCK, VEGF, and Notch pathways, in the pathogenesis of IHs. These pathways contribute to endothelial cell proliferation, migration, and survival, as well as interactions between endothelial cells and pericytes. Recent studies have also highlighted the potential influence of immune dysregulation in IH development, focusing on the role of macrophages, T cells, and cytokines in promoting angiogenesis and inflammation within the tumor microenvironment (9). While advances have been made in understanding the pathogenesis of IHs, further research is needed to uncover the intricate molecular mechanisms underlying their initiation, growth, and involution, which could potentially lead to more targeted and effective therapeutic interventions (7,9).

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Diagnostic Challenges:

The diagnosis of infantile hemangiomas (IHs) poses a multifaceted challenge owing to their heterogeneous clinical presentations and potential overlap with other cutaneous and subcutaneous conditions, common sequelae prior to initiation of therapeutic measures include ulceration (16). Consequently, accurate diagnosis and appropriate management are pivotal in preventing complications and optimizing outcomes. IHs often exhibit characteristic features, yet atypical manifestations may mimic various congenital or acquired anomalies, necessitating a comprehensive diagnostic approach. Differential diagnosis involves discriminating between IHs and vascular malformations, vascular tumors, or other dermatological conditions, particularly when IHs deviate from the prototypical raised, red appearance (13). Moreover, the natural evolution of IHs, marked by initial proliferation followed by involution, further complicates diagnostic certainty. In certain instances, IHs may also be associated with underlying syndromes or systemic anomalies, warranting a thorough evaluation to ascertain their clinical implications. Whether diagnosis occurs following an in-person or telemedicine examination, the most crucial point in diagnosis is risk stratification to initiate treatment when indicated (15, Figure 2). Integration of clinical assessment, imaging modalities such as ultrasound or MRI, and histopathological examination remains essential for accurate diagnosis and appropriate management of IHs.

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Management:

Various treatment options exist, with nonselective beta-blockers, particularly propranolol, emerging as the preferred agents. These medications have demonstrated efficacy in halting proliferation and accelerating involution. Furthermore, treatment with propranolol requires minimal monitoring, such as vital sign checks, to ensure safety during the treatment course (14). Early intervention, specialist collaboration, and tailored follow-up plans are essential for IH management, ensuring optimal outcomes and minimizing potential morbidities. Complications in management include rebound IH following a course of propranolol that may occur in roughly 25% of children, necessitating further treatment (16).

Managing infantile hemangiomas (IHs) involves a range of therapeutic approaches tailored to each lesion's specific characteristics and clinical course. Pharmacological interventions have been a cornerstone of treatment, with oral propranolol emerging as a first-line therapy for rapidly proliferating IHs (10). Propranolol, a nonselective beta-blocker, has shown remarkable efficacy in reducing hemangioma size and improving appearance. Topical beta-blockers, such as timolol, have also demonstrated success, particularly for smaller, superficial IHs (11).

Other systemic options include oral or intralesional corticosteroids, which can be effective for certain IHs, especially those less responsive to beta-blockers. Laser therapies, such as pulsed dye laser (PDL) and Nd: YAG laser, have been used to target vascular components of IHs and can benefit specific cases, particularly those with residual telangiectasia (11,12).

A multidisciplinary approach involving dermatologists, pediatricians, and other specialists may be necessary to ensure comprehensive management and minimize potential complications in complex or refractory cases.

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Conclusion:

Infantile hemangiomas (IHs) present a complex and intriguing clinical entity, necessitating a multifaceted approach to understanding their risk factors, pathogenesis, diagnosis, and management. The evolving research landscape has shed light on genetic predisposition, environmental influences, and intricate molecular pathways contributing to IH development. While diagnostic challenges arise from the diverse clinical presentations and potential overlap with other conditions, an integrated diagnostic strategy involving clinical assessment, imaging modalities, and histopathological examination remains pivotal. Management of IHs has seen significant advancements, with nonselective beta-blockers like propranolol emerging as a cornerstone treatment, complemented by other systemic options and laser therapies. The collaboration of multidisciplinary healthcare teams underscores the importance of a comprehensive approach to IH care, ensuring optimal outcomes and minimizing potential morbidities.

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