Current Management of Infantile Hemangiomas

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During the past several years, there have been new advancements in the management of infantile hemangiomas (IHs). In many patients, no treatment is ever necessary—because IHs are well known for their natural history of spontaneous involution. However, a significant minority of hemangiomas do require treatment. Moreover, they are very heterogeneous, making the decision of when, how, and why to intervene quite variable. The least common but most important rationale for intervention is the presence of a life- or function-threatening complication, where prompt therapeutic intervention is a necessity. A much more common scenario is ulceration, where appropriate management is needed to expedite healing and control pain. Increasingly, the life-altering aspects of hemangioma are being recognized as a rationale for treatment because permanent scarring and disfigurement can result even if involution is complete. Treatments for IHs currently include topical, intralesional, and systemic therapies. Laser and surgical modalities are also sometimes used depending on the clinical scenario. In the absence of rigorous evidence-based studies, clinicians must carefully weigh the risks and benefits of medical or surgical treatments versus observation alone in tailoring management to the specific clinical situation at hand.
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Infantile hemangiomas (IHs) are the most common, benign vascular tumors of infancy, present in 4% to 5% of the population.[1] Hemangiomas have a characteristic clinical appearance and predictable natural history. Most are not present, or, present only as a precursor lesion at birth. Most IHs go on to proliferate rapidly for the first several months of life, followed by a period of gradual involution. In most patients with IHs, no treatment is necessary because most lesions regress over years without leaving significant scarring. However, for some patients, hemangiomas can be complicated by ulceration, leave permanent anatomic distortion or scars, or impair function. In these cases (or where such complications are anticipated) prompt intervention is often required.

When treatment is needed and how best to administer depends on the specific clinical situation at hand. The age of the patient, location, and size of the hemangioma all have an impact on therapeutic choices, as do the anticipated complications. Because of their heterogeneity, the decision about when and how to intervene should be made on an individual basis.[2] Even in cases in which concerning features are absent or have not yet developed, which leave the rationale for treat-

ment uncertain, close follow-up and anticipatory guidance (so-called "active non-intervention") may be the best approach.[3]

Although the rationales for treating IHs are quite diverse, they are best separated into 3 distinct categories:

- to prevent or improve functional impairment or pain;
- to prevent or improve scarring and/or disfigurement; and
- to avoid life-threatening complications.

In the first category, "prevent or improve functional impairment or pain," there are many clinical situations in which this may be the rationale for treatment. Ulceration is the most common example, in which improving pain and function is achieved through treatment with appropriate wound care techniques, systemic, laser, or surgical modalities. In the second category, "to prevent/improve scarring or disfigurement," there are many clinical circumstances in which intervention may be necessary to prevent disfigurement or improve esthetic outcome for patients. In these cases, the location and size of the hemangioma have a dramatic impact on therapeutic choices (see below in "Management of Infantile Hemangiomas"). Finally, in "avoidance of life-threatening complications," such as those with airway or symptomatic hepatic involvement, anticipation of possible complications and prompt intervention can be life saving. Clinical situations, rationale for treatment, and current man-

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agement options are outlined below in Rationale for Management.

Natural History and Growth Characteristics

A thorough discussion of the management of IHs demands a working knowledge of their natural history as well as their potential associations and complications. In general, they are not present at birth but appear shortly afterward. In some cases, a precursor lesion, such as vascular patch or area of pallor/vasoconstriction, can precede hemangioma growth and may be present at birth. Hemangiomas tend to "mark out their territory" early in their development. They then proliferate within their predetermined borders and tend to grow in volume rather than diameter. During the first 3 to 5 months, superficial IH proliferate rapidly, and in most cases (80%) growth is complete by 5 months of age.[4] Deep IH often lag in growth by about 1 month compared with superficial IH, and they proliferate for (on average) 1 month longer.[4] Despite these well-defined parameters, IHs are very heterogeneous and during, the early proliferative phase, the growth characteristics of any individual IH can be difficult to predict. Some hemangiomas barely proliferate at all beyond their nascent phase. These hemangiomas have a minimal or absent growth phase.[5] At the other end of the growth continuum, some hemangiomas, particularly large ones with a deep component, have been observed to grow for longer than expected, occasionally up to 1 to 2 years.[6] This heterogeneity makes treatment decisions difficult and mandates both close observation in the first few months of life and reevaluation of advice given to parents if any unexpected growth occurs. In general, most IHs requiring treatment are best treated early in the proliferative phase when there is still time to prevent possible adverse sequelae.

Current Management of Infantile Hemangioma

There is no "one-size-fits-all" approach to the management of IHs. The decision to treat depends on the individual patient and the specific clinical scenario at hand. Treatment options are different depending on the age of the patient, size, and location of the IH. Thus, the discussion on current management of IHs is organized in the sections to follow by delineating the clinical scenarios in which treatment is warranted or necessary, describing the rationale for the intervention, and then outlining the various therapeutic modalities appropriate for the situation. Because there are no gold standard therapies and a paucity of randomized clinical trials in support of these interventions, clinical experience (or lacking that, consultation with more experienced colleagues) is extremely helpful in guiding decisions about when, why, and how to treat IHs.

Rationale for Intervention: Prevent or Improve Functional Impairment or Pain

There are several clinical situations in which IHs can cause functional impairment or pain. The most common of these is ulceration, which causes significant morbidity for affected patients. Functional impairment can develop in certain locations, such as periorbital or lumbosacral regions. Segmental hemangiomas present a greater risk of causing either functional impairment, scarring, or ulceration.

Ulceration

Ulceration occurs in approximately 15% to 25% of IHs in a referral setting.[7] Risk factors include large, segmental IHs with a superficial component, and those located on mucosal sites (lip and anogenital) or intertriginous sites (neck, perineum).[7] The average age at time of ulceration is 4 months. Most cases present with crusting or skin breakdown—typically at the center of the hemangioma—without antecedent trauma. In some cases a gray-to-white discoloration, similar to that seen in involuting hemangiomas, is evident at an unusually young age (2-3 months of age) and heralds ulceration. The best predictors for ulceration are those mentioned previously, but even in high-risk sites, such as the diaper area, 50% of hemangiomas will not ulcerate, underscoring the difficulty in predicting which IHs are going to ulcerate. However, large lesions in the high-risk locations mentioned previously and those with early whitish surface change are very likely to proceed to ulceration.

Although strategies for prevention of ulceration are not well-established, avoidance of irritation or friction, liberal use of emollients in at-risk sites, and treatment with therapies aimed at preventing hemangioma growth may help minimize ulceration. Pain and scarring are the major causes of morbidity when ulceration occurs. Although wounds readily become colonized, overt infection is uncommon to rare. Bleeding is also a surprisingly uncommon complication, with severe bleeding occurring in approximately 1% in a referral population[7] Ulceration of prereorificial sites (perioral and anogenital areas) is most concerning because of obvious functional and esthetic consequences. The management of ulcerated hemangiomas is discussed below.

Periorbital Hemangiomas Threatening Visual Compromise

Obstruction of the vision by a periorbital IHs can lead to complications, such as strabismus and amblyopia.[8] Even when the IH does not completely occlude the visual axis, pressure or mass effect on the globe can cause astigmatism. Segmental hemangiomas involving the eyelids, retro-orbital location, size greater than 1 cm in diameter, and those with upper eyelid location carry the greatest risk of complications. Infants with periorbital hemangiomas should have frequent, regular eye examinations by an ophthalmologist during the first few months of life during the proliferative phase. If visual compromise is suspected or detected, systemic therapy or surgical debulking is usually indicated.[8-10] In patients with amblyopia, patching the unaffected eye is usually recommended.[8]

Lumbosacral Hemangiomas; Possible Spinal Dysraphism or Structural Anomalies

Spinal dysraphism has been reported in association with segmental hemangiomas of the lumbosacral area. Tethered spi-

nal cord and lipomyelomeningocele have been reported, as have associated structural anomalies of the genitourinary system.[11,12] The constellation of structural anomalies in this region has been referred to by different acronyms—sacral (spinal dysraphism, anogenital, cutaneous, renal and urological anomalies, associated with an angioma of lumbosacral localization) syndrome, or PELVIS (perineal hemangioma, external genitalia malformations, lipo myelomeningocele, vesicorenal abnormalities, imperforate anus, and skin tag)—and is viewed by some as the lower-body counterpart to PHACES (ie, *p*osterior fossae abnormalities, *h*emangioma, *a*rterial/aortic anomalies, *c*ardiac anomalies, *e*ye abnormalities and sternal/supraumbilical raphe) syndrome.[13,14] Infants with large or segmental IH in the lumbosacral area should be evaluated with magnetic resonance imaging (MRI) to rule out associated anomalies. In very young infants (younger than 3 months old), MRI is insufficiently sensitive to detect tethered spinal cord. Therefore, follow-up and repeat imaging studies should be performed in patients in whom there is a high index of suspicion.

Segmental Extremity Hemangiomas

Large, segmental, or regional IHs of an extremity can be concerning because of their tendency for ulceration. Rarely, if very large or bulky, they may lead to decreased mobility. If ulceration occurs, or if the bulkiness of the lesion leads to complications, intervention may be warranted. Some patients with extensive leg IHs have also had perineal involvement with associated structural anomalies and there is at least 1 report of a large segmental hemangioma of the leg and perineum associated with genitourinary structural anomalies, arteriovenous shunting, cardiac compromise and progressive soft tissue necrosis.[15]

Rationale for Intervention: Prevent or Reduce Scarring and Disfigurement

IHs can cause permanent scarring and disfigurement and currently, this is the most common reason for initiation of treatment.[16] Involuted hemangiomas can leave behind stretched, fibrofatty or anetodermatous tissue that can be disfiguring. On prominent areas, such as the face, such changes can truly be life-altering. Certain areas on the head and neck are particularly prone to leaving scars: the nose, perioral skin, nasal side-wall, medial cheek, and ear. Segmental or very thick hemangiomas of the scalp can result in significant alopecia, but this is quite variable and hard to predict. When poor esthetic outcome is anticipated, intervention should be considered as soon as possible, with the physician weighing risks and benefits of specific treatments. Specific clinical scenarios are detailed in the subsections to follow.

Exophytic Hemangiomas and Potential Skin Textural Changes or Disfigurement

Exophytic, sessile, or pedunculated IHs with a thick dermal component, particularly when in prominent locations (head and neck), can cause significant permanent skin change. Even after involution is completed, the excessive stretching
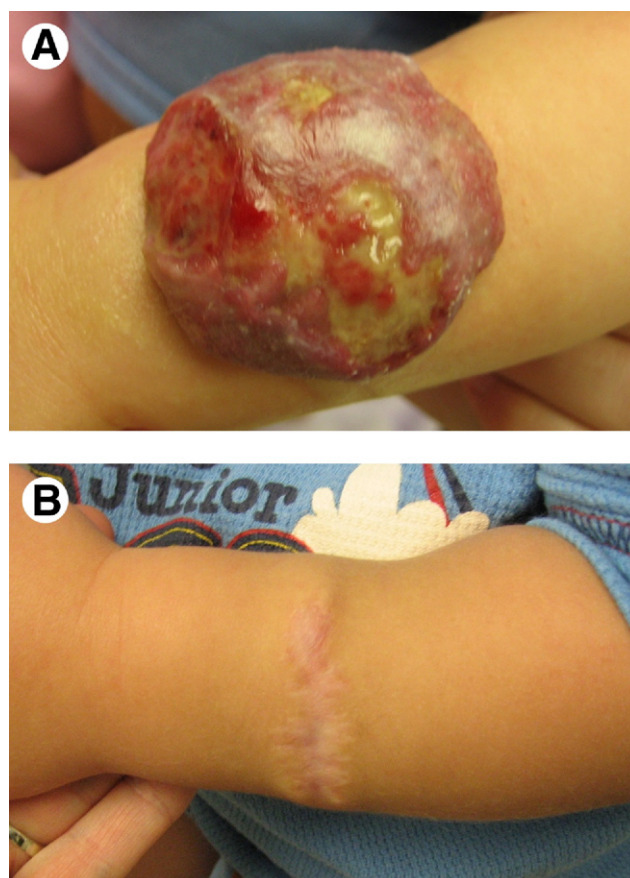

Figure 1 (A) Exophytic ulcerated hemangioma ultimately treated by early surgical excision and purse string closure. (B) Resultant scar.

of the overlying skin leads to damage in the dermal elastic tissue (anetoderma) as well as atrophy, textural change, and persistent fibrofatty residuum. With clinical experience it is often fairly easy to recognize these hemangiomas (Fig. 1), but it may not be soon enough to prevent the irreversible damage to the skin. In these cases, where such disfiguring sequelae is a certainty and the results of waiting until an older age are unlikely to produce an acceptable esthetic result, early surgical correction is a reasonable option. The use of a purse-string closure technique has been reported to help minimize the size of the resultant scar.[17]

Nasal Tip Hemangioma and Cyrano Nose Deformity

Nasal tip hemangiomas can lead to significant esthetic compromise. In its most exaggerated form, this is known as the "Cyrano" nose deformity. These hemangiomas often have a deep component resting in and around the nasal cartilage. During proliferation, this leads to splaying of the alar cartilage, and a round, bulbous appearing nasal tip. Involution is often incomplete and leaves behind fibro tatty residuum, adding to the problem. This deformity can cause significant parental anxiety and poor cosmetic outcome for the patient. Systemic therapy (either with corticosteroid or propranolol) or intralesional steroids may be helpful in preventing or minimizing permanent change in the nose.[18] If deformity persists, surgical excision before school age is also worth considering to prevent permanent affects on self-esteem.

Segmental Facial Hemangioma; Risk of PHACE Syndrome and/or Risk of Skin Textural Changes

Patients with large, segmental facial IH are at risk for both adverse esthetic outcomes and associated structural anomalies. The association of PHACES is a well-documented neurocutaneous phenomenon,[19] and diagnostic criteria defining the syndrome have recently been proposed.[19] Prospective studies of patients with large facial hemangiomas have found a risk of approximately 30% with segments 1 and 3 being at highest risk for PHACE.[19-21] This suggests that all patients with large facial hemangiomas involving these segments should have a complete evaluation for PHACE, including MRI and MR arthrography of the head and neck, echocardiogram, ophthalmologic examination, and thyroid studies. Many but not all patients with segmental facial hemangiomas also require systemic therapy to prevent functional compromise (ie, ulceration, visual compromise, airway disease) and to preserve normal facial anatomy.

Rationale for Intervention: Avoid Life-Threatening Complications

Airway Hemangioma

Segmental hemangiomas, particularly those located in the mandibular area, carry a high risk of associated airway hemangiomas. Affected infants typically present with noisy breathing, hoarse cry or stridor, most often in the first 4 to 12 weeks of life. Airway hemangioma represents one of the most serious, potentially life-threatening complications of IH. Identifying high-risk patients and instituting multidisciplinary management in conjunction with pediatric otolaryngology is essential. Endoscopic laryngoscopy is helpful in identifying airway lesions, and in some cases otolaryngologists are able to intervene with laser ablation during the procedure.[22] First-line treatment with high-dose (3-5 mg/kg/d) systemic steroids with laser as an adjunctive therapy is usually instituted.[23,22] However, the authors of several reports[24,25] have now shown that oral propranolol can be highly effective in treating airway hemangiomas even in cases in which steroids have been insufficiently effective. (See the section "Systemic Therapy for Infantile Hemangiomas.")

Symptomatic Liver Hemangiomas

The liver is the most common extracutaneous site of IH. Infants with >5 IH should be evaluated for the possibility of liver hemangiomas via hepatic ultrasound. Even if present, hepatic hemangiomas are often asymptomatic; however, a minority cause morbidity and in rare cases are life-threatening. A classification for liver hemangiomas has been proposed by Christison-Lagy et al, including 3 types of hepatic hemangiomas, 2 of which are true IHs.[26-29] The most common, multifocal liver hemangiomas may cause high-output congestive heart failure. A rarer form, diffuse liver hemangiomas which fill the entire liver, are associated with threat of abdominal compartment syndrome, and a severe form of hypothyroidism attributable to tumor-related deiodination of thyroid hormone.[30] A third type of hepatic hemangioma, the solitary liver hemangioma, often presents at birth with arteriovenous shunting and in most cases are not true IHs but more likely a form of rapidly-involuting congenital hemangioma occurring in the liver.[26]

When cardiac compromise or severe hypothyroidism is a complication of hepatic hemangioma, systemic or surgical intervention is necessary. In very rare cases in which life-threatening complications occur, even liver transplant may be considered as a therapeutic option.

Understanding *which* hemangiomas require treatment and *when* a specific intervention will be of benefit is necessary for appropriate management. Historically, in the 1940s through 1960s, hemangiomas were treated aggressively with radical surgeries and/or radiation, as their true natural history was not well understood. Subsequently, when the natural history and growth characteristics of hemangiomas became better elucidated by Jacobs,[31] the pendulum swung to an antiinterventionist approach on the basis of studies that showed that *no* intervention often resulted in better cosmetic outcome than available treatments used at the time. Corticosteroids as a medical therapy for IH were introduced in the 1960s, and became a mainstay of therapy, but have been used without robust randomized controlled trials. There are no medications approved by the Food and Drug Administration for treating IH. However, during the last few years some new advances have been made in medical therapy, and some studies are underway.

"Active Nonintervention"

The vast majority of IHs do not require treatment, given their natural history of involution over time. However, in today's information-rich environment, even parents of infants with relatively low-risk IH, particularly in prominent locations, often seek out treatment. Disturbing/intrusive comments from friends, family members, and/or strangers can result in parental guilt or shame, leading to the desire for active intervention.[32] Rather than "benign neglect," we prefer the term "active non-intervention" to describe the management of IH in which active treatment may not be necessary but close observation with periodic office visits is essential. In addition, active nonintervention implies that clinicians/caregivers acknowledge parental stressors and spend time educating parents about the heterogeneity and natural history of IH, helping them to understand why no treatment is often the most appropriate course of action in most cases. Comparing serial photographs is also essential for accurately assessing growth and should be performed at each visit.

In some patients in whom it is not clear initially whether therapy will be needed, frequent follow-ups are particularly important. Not all high-risk lesions need treatment because some demonstrate less rapid or aggressive growth. In addition to a discussion on their natural history, clinical photographs, hemispheric measurements, before/after photographs and frequent follow up can help to reduce parental stress. The role of the Internet in parental self-education or Internet support sites surrounding hemangiomas also deserves consideration when educating families about IH. Encouraging parents and providing them with reputable sites/resources can help in supporting affected families.[33]

Current Management of Ulcerated Hemangiomas

Ulceration is the most common complication of IH. Like other aspects in the management of IH, there is no "gold standard" therapy for ulceration, and a lack of evidence-based studies to support specific interventions. In general, topical modalities, such as barrier emollients like petrolatum or Aquaphor in conjunction with nonadherent dressings, such as thin hydrocolloid dressings or petrolatum impregnated gauze are used as first line therapies. An important practical point is that the fibrinous or hemorrhagic crust at the surface of ulcerated IH blocks reepithelialization and can be a source for bacterial superinfection. Removal of the crust with dilute hydrogen peroxide soaks is recommended. Ulcerated hemangiomas should not be assumed to be infected (although are often colonized). Anecdotally, metronidazole gel has been reported to be effective as an adjunctive treatment particularly in perioral, neck fold, and perianal ulceration. Overt bacterial infection is uncommon but if a heavy or malodorous exudate, pustules or erythema and induration of surrounding skin is present, bacterial cultures should be obtained and appropriate systemic antimicrobials initiated as appropriate.

Becaplermin (topical platelet-derived growth factor) gel has been reportedly effective in expediting healing of ulcerated hemangiomas and can be used as a second line therapy.[34,35] The Food and Drug Administration applied a boxed warning for this agent because of reports of increased risk of cancer-related deaths in adult leg ulcer patients. No increased incidence in cancer has been found in treated patients, and many pediatric dermatologists feel that this warning is less likely to apply to the pediatric population; however, it does reinforce its second line role in the therapeutic ladder for ulcerated hemangiomas.[36]

The flash lamp-pumped pulsed dye laser (PDL) is another modality which is helpful in relieving pain and expediting healing in the setting of ulceration.[37,38] Early surgical excision in painful ulcerated lesions in which a scar is inevitable is also an appropriate therapeutic consideration (Fig. 2). In addition, oral propranolol has been described in the management of ulcerated hemangiomas[39]; however, further studies are needed to evaluate efficacy and safety. Propranolol as a systemic treatment for IH is discussed in detail below.

Topical Therapy (Corticosteroids, Imiquimod, Timolol)

No large clinical trials exist in support of any topical therapy in the management of IHs. Some case reports/series demonstrate some evidence for certain modalities, mainly during the early proliferative phase of growth of very superficial IH, however mixed or deep IH typically do not respond to topical therapies. The advantage of topical therapies is their lack of systemic effect, although when used in larger amounts (in larger hemangiomas), significant systemic absorption remains a real possibility. Their disadvantage is limited penetration that may preclude effectiveness for thicker or deeper lesions, including those which may appear to be superficial

Figure 2 (A) Segmental hemangioma of the labia, inguinal crease and medial thigh with significant painful ulceration. (B) Complete healing status post conservative wound care (vaseline, metrogel and dressings), pulsed dye laser and oral propranolol.

but have an occult or emerging deeper component. Super potent topical steroids, particularly clobetasol, have shown some benefit in treating relatively small, superficial IH—particularly in the periorbital distribution.[9,40,41] Potential side effects include possible systemic absorption, cutaneous atrophy and striae, so close follow-up is warranted. Topical imiquimod has also been reported safe and effective in treating some small superficial lesions[42-44] and could be considered as a treatment option in patients presenting in the early proliferative phase with IH on visible locations. Crusting and theoretically, ulceration, are possible complications. A topical β-blocker, timolol 0.5% gel or solution, has been reported to be effective in treating small, superficial IH (Pope et al, abstract, pediatric dermatology meeting, Philadelphia, 2009).

Intralesional Therapy (Corticosteroids)

Intralesional steroids for the treatment of IH were originally described by ophthalmologists for the management of periorbital lesions.[45] Because of the risk of retinal artery damage and blindness, this treatment fell out of favor among ophthalmologists.[46] Intralesional steroids for IH on other sites (nasal tip, lip, and other sites) can be effective, particularly when administered during the proliferation phase, and in small tumors where the medication will be more likely to distribute evenly.[47] The dose of steroid, usually triamcinolone, should

not exceed a maximum of 1 to 2 mg/kg per treatment (to a maximum of 10 mg).[3] Several treatments, spaced at 3- to 6-week intervals, are often needed. We generally recommend triamcinolone 10 mg cm^{-3} rather than more concentrated forms. Potential side effects include bleeding, skin atrophy, and in rare cases skin necrosis, infection, anaphylaxis, and adrenal suppression.

Systemic Therapy (Systemic Corticosteroids, Propranolol, Interferon, Vincristine)

Systemic therapies are needed in cases in which hemangiomas cause life- or function-threatening complications, providing us with a rationale for treatment. At this time, the mainstay of treatment is still systemic corticosteroids, but recently, oral propranolol has shown great promise as an effective systemic therapy. In addition, vincristine and alpha-interferon can also be considered in certain cases or added in conjunction with other modalities. None of these systemic medications are approved by the Food and Drug Administration for this indication. A double-blind placebo-controlled trial to assess the efficacy of propranolol is currently underway (see http://www.clinicaltrials.gov for more information).

Systemic corticosteroids (prednisolone, prednisone) have been the mainstay of therapy for hemangiomas since their efficacy was serendipitously discovered in the 1960s.[48,49] Systemic corticosteroids are usually dosed between 2 and 3 mg/kg/d of prednisolone, depending on the clinical situation. The authors of a relatively small randomized controlled trial[50] found that daily oral steroids were more effective than pulsed intravenous methylprednisolone. A meta-analysis demonstrated that 3 mg/kg may be more effective and stabilization of growth was achieved in 90% of cases, whereas actual shrinkage occurs in only one third of cases.[51] These findings suggest that systemic steroids are most likely to be effective if given during the proliferative phase, typically during the first 1 to 4 months of life. The average duration of treatment is 6 months. Potential side effects include gastrointestinal upset and irritability, which can be ameliorated with H2 blockers, such as ranitidine, 2-4 mg kg^{-1} d^{-1} divided twice daily. Weight gain, moon facies/cushingoid appearance, and hypertension are also potential adverse effects as are delayed growth, adrenal suppression and immunosuppression.[52,49] Catch-up growth occurs in most cases, and despite this formidable list of potential side effects, most infants tolerate therapy well, without severe health issues.[53] A rare potential adverse effect is systemic infection. Rare cases of *Pneumocystis pneumoniae* have been reported during therapy.[54,55] Prompting many physicians to give prophylactic doses of trimethoprim/sulfamethoxazole (5-10 mg/kg of trimethoprim divided twice daily 3×/wk) while on steroid therapy. Regular, frequent follow-up of infants treated with systemic steroids—typically once monthly—is recommended until the corticosteroids are weaned. Switching to alternate day therapy during the weaning period may help in adrenal recovery and improved linear growth. Recent studies have shown that the effect of systemic steroids on bone density and adrenal axis suppression in young infants are not usually severe and should not impede treatment.[52]

Oral propranolol is the most recent systemic therapy for treating IH and preliminary reports of efficacy are extremely promising, with more predictable shrinkage of hemangioma tissue, even after the growth phase is completed.[56] Propranolol is a nonselective beta adrenergic blocker. It has been used in infancy primarily as a treatment for cardiac conditions and neonatal hyperthyroidism. Its use for IH was unanticipated, but it was observed to shrink a hemangioma in a child with steroid-induced hypertension, and then tried on larger numbers of patients to verify its effects. Since the initial report of its use, published in 2008, many more reports have confirmed beneficial effects in IH involving the skin but also the liver,[57] airway,[24] for skin ulceration[39] and for high-risk periorbital hemangiomas.[58] Doses have typically been in the range of 1-3 mg/kg divided two or three times daily.

The mechanism of action of propranolol in hemangiomas is not known, but some authors speculate that there may be increased apoptosis and down-regulation of vascular endothelial growth factor as the result of vasoconstriction.[59,60] Despite this initial promise and speculation by many clinicians that propranolol may usurp oral corticosteroids as the treatment of choice for IH, there are many potential side effects of propranolol, including hypoglycemia, hypotension, and bradycardia.[61] An additional concern has been raised in infants with PHACE syndrome with structural anomalies of the cerebrovasculature, such as tortuous, aneurysmal, or stenotic intracranial arteries who could at least theoretically be at increased risk of stroke if treated with propranolol. It is prudent that infants with large facial hemangioma be evaluated for PHACE association before initiation of oral propranolol whenever possible. Adverse events, including bradycardia and hypoglycemia have already been reported in a handful of cases.[60] Until larger clinical trials are completed, consultation with a pediatric cardiologist to determine the safest regimen is advised.

Recombinant interferon alpha (2a and 2b) has known antiangiogenic properties, and many reports attest to its efficacy in treating IH, particularly in complicated hemangiomas which have failed to respond to oral corticosteroids. However, since the recognition of serious neurologic sequelae (spastic diplegia, up to 20% of treated patients), most authors have reserved this as a second- or even third-line treatment.[62] Other side effects of interferon include flulike symptoms, neutropenia, and transaminitis. Interferon use is generally reserved for severe cases causing life-threatening complications when high-dose corticosteroids and/or other medical therapies are not effective. Potential neurotoxicity appears to decrease with increasing age, and is rarely reported after age 1, so interferon can be useful in the treatment of older children (>1 year of age), particularly those with prolonged growth phase causing medical morbidities, such as failure to thrive.[6]

Vincristine is a vinca alkaloid microtubule inhibitor that is used primarily by oncologists to treat hematologic and solid tumor malignancies. There are several case reports documenting the benefit of vincristine for the treatment of life or function threatening IH.[63,64] In this setting, vincristine is

given intravenously at a dose of 1.0 to 1.5 mg m^{-2} weekly. Vincristine has many known side effects when used at high doses as a chemotherapeutic agent, including immunosuppression, neuropathy, and alopecia. However, in most of the cases reported, there was good response to treatment with a favorable safety profile in most patients.[63,64]

The flash lamp pumped PDL initially at wavelengths of 585 nm and at 595 nm is the most common laser modality employed in the treatment of IHs. It is best viewed as a "local therapy" as its efficacy is generally limited to superficial aspects of the disease. It is useful in lightening the brightly erythematous superficial component of IH or residual telangiectasias left behind after involution. In addition, PDL can be very helpful in expediting healing of ulcerated hemangiomas (see discussion above in "Management of Ulcerated Hemangiomas"). Although the PDL can significantly lighten the red color of IH, complications, such as ulceration and scarring have been reported in cases where treatment is initiated during the proliferative phase.[65] This is particularly concerning in large or segmental IH, which have a greater risk of ulceration in general and which often require systemic therapy because of their greater risk of complications and potential for more aggressive growth. A randomized controlled study in which the authors compared small hemangiomas left untreated versus those treated with PDL without the benefit of current skin-cooling techniques showed no real benefit at age 1 year. Other studies have shown benefits without significant scarring, but the role of laser remains controversial.[66] The bare-fiber neodynium-yttrium–aluminum-garnet (Nd-YAG) laser has been reportedly effective in treating subglottic and mixed or deep cutaneous hemangiomas.[67,68] Nd-YAG laser is more effective in deeper lesions as it has a greater depth of penetration. This method may be particularly effective in rapidly proliferating periorbital hemangiomas causing visual compromise, but it has not gained wide acceptance as a standard modality of treatment.[68]

Surgical management of IHs should be considered depending on the specific case and anticipated complications. Some IHs are amenable to early excision, whereas for others, waiting several years until involution is complete may be more appropriate. Surgical intervention is best performed by an experienced surgeon with a good knowledge of their natural history. Rationale for early surgical intervention (ie, age < 3 years) would include the following clinical situations: pedunculated or exophytic hemangiomas in which scarring is highly probable, chronically ulcerated hemangiomas causing pain, hemangiomas that will lead to significant disfigurement, or rarely, for excessive bleeding.

Like the medical therapies discussed previously in this article, there is no "gold standard" for when and how surgical intervention should be performed; it depends on the specific clinical situation at hand. Some patients may require surgery early during the proliferative phase, such as in ulcerated or bleeding IHs, or in those in whom surgical excision may help to decrease the likelihood of visual complications. Surgical management of disfiguring hemangiomas should be considered before the patient reaches school age. In cases in which the clinical outcome is not predictable, waiting longer or

consulting with a multidisciplinary vascular anomalies team can be helpful. Many children with significant facial disfigurement may need multiple procedures. A circular, purse string closure for excision of IH has been reported to minimize the length of the resultant scar, making it an excellent option for exophytic hemangiomas in prominent locations.[17]

Conclusions

IHs are very common; however, their complications depend on the size, location, and growth characteristics of the particular lesion. Given their inherent heterogeneity, developing a rationale for interventions can be challenging; however, management of individual lesions should ultimately be determined on the basis of on an in-depth knowledge of their natural history. In cases in which the rationale for treatment is unclear, seeking consultation with multidisciplinary vascular anomalies teams, if available, can be extremely helpful, particularly in life-threatening cases. Although most hemangiomas never require intervention, when needed, there are many therapeutic options available. We are optimistic that with more experience and recent advances in our therapeutic armamentarium, future management of IH will be more successful in preventing scarring, disfigurement, and life or function threatening sequelae.

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