

Guidelines of Care for Cutaneous Haemangiomas

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Abstract

Introduction: Haemangiomas are common benign tumours of the vascular endothelium. They are extremely heterogenous clinically, with size, location and rate of proliferation having a significant effect on the risk of complications. **Materials and Methods:** The available evidence in the literature was evaluated using the grading system currently employed by the Ministry of Health, Singapore. **Results:** An uncomplicated haemangioma can be observed for spontaneous involution. However, some haemangiomas may be life- or function-threatening, or have associated structural anomalies. Corticosteroids may be used topically, intralesionally or systemically. Interferon alpha, vincristine and cyclophosphamide are therapeutic options for complicated haemangiomas which do not respond to corticosteroids. Vascular-specific pulse dye laser therapy may be considered for superficial haemangiomas, ulcerated haemangiomas or post-involution sequelae like telangiectasia. The mainstay of therapy for ulcerated haemangiomas is good local wound care, analgesics and treatment of secondary infection. A periorbital haemangioma that obstructs the visual axis or exerts pressure on the globe is an ocular emergency. Systemic corticosteroids and patching of the unaffected eye should be considered. **Conclusions:** Medical practitioners should be aware of available therapeutic options for life- or function-threatening haemangiomas. Treatment must be individualised and referral to the relevant specialist should be considered in patients with complicated haemangiomas.

Ann Acad Med Singapore 2005;34:117-23

Key words: Cyclophosphamide, Interferons, Lasers, Steroids, Vincristine

Introduction

In 1982, Mulliken and Glowacki classified vascular anomalies into tumours and malformations.¹ A modification of this classification was adopted by the International Society for the Study of Vascular Anomalies in 1996.² A clear distinction was drawn between vascular tumours, which are characterised by endothelial proliferation, and malformations, which are true errors in vascular morphogenesis with little endothelial mitotic activity.

A haemangioma is a benign vascular tumour. Studies in the Caucasian population revealed that haemangiomas of infancy are found in 1.1% to 2.6% of term neonates and their prevalence is estimated to be as high as 10% to 12% in infancy.³⁻⁵ They occur in children of all races, but are less common in those of African or Asian descent. Haemangiomas occur about 3 to 5 times more frequently in females and are particularly common among premature infants. In our experience, it is the commonest childhood

vascular tumour seen in Singapore, but the incidence is lower than that of the Caucasian population. Other vascular tumours, e.g., pyogenic granuloma, tufted angioma, kaposiform haemangioendothelioma, are less commonly seen in children; the latter 2 tumours are rare.

The pathogenesis of haemangiomas remains poorly understood. An interesting theory proposed by North et al⁶ suggests that haemangiomas may originate from either invading angioblasts that differentiate toward a placental phenotype, or from embolised placental cells. GLUT1 is a glucose transporter which is uniquely expressed in the endothelial cells of haemangiomas. It is also expressed in the microvascular endothelia of the placenta, but not in normal skin or other vascular lesions such as malformations, pyogenic granuloma or granulation tissue. Haemangiomas also demonstrate immunoreactivity with other placenta-associated vascular antigens such as Lewis Y antigen and merosin.

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Haemangiomas can be extremely heterogenous clinically and present as diagnostic challenges. We have reviewed the literature and, based on the evidence and our local experience, we present recommendations on appropriate therapies for haemangiomas.

Methodology

The electronic database MEDLINE was used to search the medical literature for publications containing the key words “haemangioma”, “therapy” and then cross-referenced with each of the treatment modalities found. Publications in foreign languages were included if they had abstracts in English. The available evidence was evaluated using the grading system currently employed by the Ministry of Health, Singapore (Tables 1 and 2).

Types of Haemangiomas and their Clinical Features

1. Haemangioma of Infancy (HOI)

These are the most common type of haemangiomas. They appear within the first few weeks of life and have a predilection for the head and neck. They demonstrate rapid growth in early infancy, usually from 3 to 6 months of age, and subsequently, slower growth to their maximum size at approximately 9 to 12 months of age. They then enter the involution stage, which may begin anytime between a few months to 18 months of age.⁷ During involution, the superficial component undergoes a colour change from bright red to dull red, then to grey; the deep component becomes less blue and less warm. HOIs complete involution at the rate of 10% per year and 50% show no clinical trace at complete resolution. However, 50% of HOIs resolve with minor residual changes like telangiectasia, atrophic wrinkling and discolouration, or more cosmetically significant changes like excess skin with underlying fibrofatty tissue or scarring. The histopathological picture of HOIs evolves as they mature: a mass of endothelial cells

Table 1. Levels of Evidence

Level	Type of Evidence
Ia	Evidence obtained from meta-analysis of randomised controlled trials.
Ib	Evidence obtained from at least one randomised controlled trial.
IIa	Evidence obtained from at least one well-designed controlled study without randomisation.
IIb	Evidence obtained from at least one other type of well-designed quasi-experimental study.
III	Evidence obtained from well-designed non-experimental descriptive studies, such as comparative studies, correlation studies and case studies.
IV	Evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities.

in the early proliferative phase, subsequent development of lumens lined by normal endothelial cells and finally the lobules of endothelial channels are separated by fibrous septae.

Worrisome presentations and their associated complications are summarised in Table 3. An HOI located on the lower face and anterior neck may be associated with a symptomatic airway haemangioma. Infants with HOIs in this location should be monitored closely for stridor, especially during feeding or crying, cough, cyanosis and hoarseness, particularly in the first 3 months of life. In a symptomatic infant, direct laryngoscopy is the most rapid

Table 2. Grades of Recommendation

Grade	Recommendation
A (evidence levels Ia, Ib)	Requires at least 1 randomised controlled trial as part of the body of literature of overall good quality and consistency addressing the specific recommendation.
B (evidence levels IIa, IIb, III)	Requires availability of well-conducted clinical studies but no randomised clinical trials on the topic of recommendation.
C (evidence level IV)	Requires evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities. Indicates absence of directly applicable clinical studies of good quality.

Table 3. Worrisome Presentations of Haemangiomas and Associated Complications

Anatomic location, morphology	Associated complication
“Beard area” and neck	Airway obstruction
Periorbital	Ocular axis occlusion, amblyopia, astigmatism
Lip, perioral, anogenital, intertriginous area	Ulceration, difficulty with feeding, micturition or defecation
Nasal tip	Partial/slow involution
Large segmental haemangioma on the face	PHACES syndrome
Lumbosacral spine, anogenital	Tethered spinal cord, lipomeningomyelocele, genitourinary anomalies
Ear, parotid	Otitis, decrease in auditory conduction
Multiple haemangiomas	Visceral involvement (especially liver, gastrointestinal tract), congestive cardiac failure
Very large haemangioma, hepatic haemangiomas	Hypothyroidism

way to confirm a diagnosis of airway compromise.

2. *Non-involuting Congenital Haemangiomas*⁸

These haemangiomas are rare and present as solitary pink to purple tumours, often with coarse telangiectasia on the overlying skin. They are warm, round to ovoid in shape and have a central or peripheral pallor. They proportionately increase in size with the growth of the child but do not involute. Their characteristics on magnetic resonance imaging (MRI) are similar to those of HOIs. Histopathologic examinations reveal lobular collections of small, thin-walled vessels with a large, often stellate, central vessel. Interlobular areas contain predominantly dilated, often dysplastic veins; arteries are also increased in number. Small arteries are observed “shunting” directly into lobular vessels or into abnormal extralobular veins. “Hobnailed” endothelial cells line the small intralobular vessels. There is an increase in the number of mast cells.

3. *Rapidly Involuting Congenital Haemangiomas*^{9,10}

These rare haemangiomas proliferate in utero, are fully developed at birth and begin to regress during early infancy. They may present as a) violaceous tumours with ectatic veins, b) grey tumours with multiple tiny telangiectasia and a surrounding pale halo, or as c) violaceous flat infiltrative tumours. The histopathologic picture shows small-to-large lobules of capillaries with moderately plump endothelial cells and pericytes; the lobules are surrounded by abundant fibrous tissue. Some specimens show a central involuting zone characterised by lobular loss, fibrous tissue, and draining channels that are often large and abnormal. Ancillary features commonly found include haemosiderin, thrombosis, cyst formation, focal calcification, and extramedullary haematopoiesis. They regress by 14 months of age, leaving either atrophic or redundant skin.

4. *Multifocal Haemangiomas With or Without Extracutaneous Involvement [also known as benign neonatal haemangiomatosis (cutaneous-limited), disseminated neonatal haemangiomatosis (visceral involvement)]*

This is a rare presentation in which multiple small cutaneous lesions, varying in size from a few millimetres to several centimetres, are found in the neonatal period. There is an associated risk of visceral involvement, especially in the liver and gastrointestinal tract, which may in turn lead to congestive cardiac failure and haemorrhage. Findings suggestive of hepatic involvement include hepatomegaly and a hepatic bruit. Tachypnea and respiratory crepitations may suggest cardiac failure.

5. *PHACES syndrome*¹¹

Children with this rare syndrome present with a large facial haemangioma and associated abnormalities, which include:

- Posterior fossa malformation
- Haemangioma (large facial)
- Arterial anomalies
- Cardiac anomalies
- Eye anomalies
- Sternal cleft +/- supraumbilical raphe.

Differential Diagnoses

The differential diagnoses include, but are not limited to:

1. other vascular tumours e.g., pyogenic granuloma, tufted angioma, kaposiform haemangioendothelioma;
2. vascular malformations e.g., port-wine stain, venous/lymphatic/arteriovenous malformation;
3. non-vascular benign tumours e.g., nasal glioma, myofibromatosis, Spitz naevus, dermoid cyst; and
4. non-vascular malignant tumours e.g., rhabdomyosarcoma, fibrosarcoma.

It is now known that Kasabach-Merritt syndrome does not occur in haemangiomas.¹² Instead, this platelet consumption syndrome is a complication of 2 much less common vascular tumours, namely, kaposiform haemangioendothelioma and tufted angioma.¹³

Investigations

In the vast majority of cases, the diagnosis can be established on the basis of history and physical examination alone. The following diagnostic tests may be considered in clinically atypical cases:

1. *Skin Biopsy*

The increased risk of bleeding makes this a relatively risky way to make a diagnosis. However, it is occasionally necessary to differentiate atypical cases from other soft tissue tumours e.g., kaposiform haemangioendothelioma, myofibromatosis and rhabdomyosarcoma.

2. *Ultrasound*

This is helpful for

- identifying hepatic haemangiomas;
- evaluating infants (less than 3 to 6 months of age, before closure of the posterior fontanelle) with large facial haemangiomas, for possible structural brain abnormalities to rule out PHACES syndrome.

3. *Magnetic Resonance Imaging*

This is useful in differentiating haemangiomas from vascular malformations. It helps to delineate the extent of the tumour in danger areas like the “beard area” (lower face/neck) where airway compromise may occur. It can be used to evaluate infants with large facial haemangiomas for possible structural brain abnormalities. On MRI and computed tomography, haemangiomas appear as well-circumscribed, lobulated masses with feeding and draining

vessels at the centre and periphery. Flow voids are seen on MRI and enhancement with gadolinium is diffuse.

4. Computed Tomography

It has the same uses as the MRI, but is not as specific in differentiating haemangiomas from vascular malformations.

5. Other Investigations

Thyroid function screening should be considered for infants with either very large haemangiomas or hepatic haemangiomas. Huang et al¹⁴ reported a 3-month-old infant with a massive hepatic haemangioma and primary hypothyroidism. High levels of type 3 iodothyronine deiodinase activity were found in the haemangioma tissue. This enzyme is involved in the inactivation of thyroxine.

Useful investigations to exclude complications in multifocal haemangiomas include full blood count, liver function test and stool occult blood test. The presence of anaemia and/or blood in the stools would raise the suspicion of a bleeding gastrointestinal haemangioma. An elevated serum alkaline phosphatase level may indicate the presence of a hepatic haemangioma.

Clinical Approach and Goals of Management

Clinical heterogeneity and the difficulty in predicting the course during early infancy make the management of haemangiomas a potentially challenging one. In the clinical approach, the physician must first differentiate between uncomplicated and complicated haemangiomas. An uncomplicated haemangioma, which refers to a haemangioma that is asymptomatic, non-ulcerated and does not have the potential to impair a vital function, can be observed. A complicated haemangioma is one that is symptomatic, potentially function- or life-threatening or one that may lead to cosmetic disfigurement and subsequent social stigmatisation. Such a haemangioma should be treated. It is often difficult to predict the progress and prognosis of the haemangioma during the first few months of life. One should monitor haemangiomas closely for the first few weeks to months with measurements and photographic documentation. The parents should be advised to return if there is unusually rapid growth or complications occur.

After making the decision to treat, the physician must select the most appropriate treatment for a complicated haemangioma, taking into account the medical status of the patient, the location and size of the haemangioma, the urgency of treatment, as well as the risks and benefits of the treatment modality. The goals of management are to: 1) prevent or reverse any threats to life or function, 2) prevent permanent disfigurement due to post-involution residual skin changes, 3) minimise psychosocial distress for patient and family, 4) prevent or treat ulcerated haemangiomas to

reduce scarring, infection, bleeding and pain and 5) avoid aggressive treatment of haemangiomas that are likely to have an excellent prognosis if left alone.¹⁵

Management

It is often difficult to predict the progress and prognosis of haemangiomas during the first few months of life. One should monitor haemangiomas closely for the first few weeks to months with measurements and photographic documentation. Such close follow-up visits also allow the doctor to provide the parents and relatives with emotional support. The parents should be advised to return if there is unusually rapid growth or complications occur. Both the physician and parents can afford to worry less after 6 months and much less after 1 year.

In our practice, we treat haemangiomas that are:

- a) compromising, or have the potential to compromise, vital functions (e.g., obstructing the airways or impairing vision);
- b) symptomatic (e.g., ulcerated, painful, bleeding, infected); or
- c) expected to involute slowly or incompletely with significant cosmetic disability (e.g., nasal haemangioma, large haemangioma).

First-line Therapy

1. Systemic Corticosteroid (B, III)¹⁶⁻¹⁸

The mechanism of action of corticosteroids is not well known, but vasoconstriction, hormonal influences and inhibition of angiogenesis have been proposed.

The response to systemic corticosteroids is variable: 1/3 of treated haemangiomas show dramatic shrinkage, 1/3 have their growth rate stabilised and the remaining 1/3 show minimal or no response. Cessation of growth or the onset of involution is usually seen within 2 weeks if the tumour is steroid-responsive. Systemic corticosteroid is our therapy of choice for haemangiomas that are compromising, or have the potential to compromise, vital functions e.g., subglottic haemangiomas and periorbital haemangiomas. As a guide, the following dosing regimen of oral prednisolone can be considered and should be tailored to the patient's response:

- 2 to 4 mg/kg for 2 to 4 weeks
- 0.5 to 1.5 mg/kg for 4 to 8 weeks
- Taper off over 4 to 8 weeks

Potential side effects include pituitary-adrenal axis suppression, Cushing syndrome, personality changes, delayed skeletal growth, gastritis, hypertension and immunosuppression. We routinely prescribe oral cimetidine (20 mg/kg/day) prophylactically to prevent gastritis. During corticosteroid therapy, we review the child at 2- to 4-week intervals. During each visit, we look out for infections and

monitor the blood pressure, height and weight of the child. For several months after the cessation of therapy, there is a need for “stress” doses of corticosteroids if the child is sick. Aseptic necrosis of the femoral head, osteoporosis and cataracts are uncommon complications if oral corticosteroids are given for a period of less than 6 months. Live attenuated vaccines are contraindicated during the period of treatment.

2. Intralesional Corticosteroids (B, III)¹⁹

Intralesional corticosteroids can be used for well-defined haemangiomas during the proliferative phase to retard their growth and hasten involution. We perform 2 to 5 intralesional injections at 4- to 8-week intervals, using EMLA cream as a topical anaesthesia. Triamcinolone, at a concentration of 10 to 20 mg/mL, can be given in doses of up to a maximum of 3 mg/kg per treatment session. Cutaneous atrophy and pain during injection are possible side effects. Intralesional corticosteroids are not recommended for periocular haemangiomas as eyelid necrosis and central retinal artery occlusion are potential serious complications.²⁰

3. Topical Corticosteroids (B, III)^{21,22}

The use of topical corticosteroids is of clinical interest. We use intermediate- to high-potency topical corticosteroids to retard the growth and reduce the size of haemangiomas that are cosmetically significant but not life- or function-threatening. There are some data in the literature to support their efficacy and they are relatively safe if used cautiously under medical supervision. The patient should be warned of adverse reactions like cutaneous atrophy and striae.

Second-line Therapy

1. Interferon Alpha-2a and 2b (B,III)²³⁻²⁵

This inhibits angiogenesis. It is given subcutaneously at a dose of 1 to 3 million units/m² body surface area daily for life-threatening haemangiomas that have failed to respond to systemic corticosteroid therapy. Treatment is usually continued for 2 to 12 months. Adverse effects include transient neutropenia, fever, elevated liver enzymes and flu-like symptoms.

Neurotoxicity, particularly spastic diplegia, is the most feared complication; this may develop in 5% to 10% of patients. Regular monitoring of the neurological status, full blood count and liver function test should be performed during treatment.

2. Vincristine (B, III)^{26,27}

There are several anecdotal reports of its efficacy in treating large, life-threatening haemangiomas. The usual dosage is 0.05 mg/kg in infants weighing less than 10 kg,

or 1.5 mg/m² in infants weighing more than 10 kg. This is given intravenously on a weekly basis via a central venous line.

Adverse reactions to vincristine are dose-related and reversible. The dose-limiting adverse effect is neurotoxicity, the severity of which varies greatly among patients. The most frequent manifestation is peripheral neuropathy and the earliest sign is asymptomatic depression of the ankle tendon reflex. Cranial nerve palsies, ataxia, bladder atony and paralytic ileus have been reported. Other adverse reactions include alopecia, rash, constipation, local reactions like phlebitis and necrosis and uncommonly, myelosuppression. Regular neurological examination of the infant and full blood count should be done during treatment.

3. Vascular-specific Pulse Dye Laser (B, III)²⁸⁻³¹

Due to the limited depth of penetration (about 1.2 mm), this laser is more effective for thin superficial haemangiomas than those with a deep component. It can improve residual telangiectasia after involution and may be effective in treating ulcerated haemangiomas. Multiple treatment sessions at 2- to 4-week intervals are required to achieve significant improvement. In our experience, adverse effects of the pulse-dye laser with an incorporated dynamic cooling device include a bruise-like appearance for up to 2 weeks and dyspigmentation; blistering and scarring are uncommon in skilled hands.

4. Surgical Excision (B, III)^{32,33}

This may be considered for well-localised function-impairing haemangiomas not responding to medical treatment, as well as lesions complicated by persistent bleeding or ulceration.

Haemangiomas may involute completely but leave cosmetically significant changes like telangiectasia, atrophic wrinkling, discolouration, redundant skin with underlying fibrofatty tissue or scarring. Surgical excision can be offered to such patients for cosmetic improvement, preferably before the child goes to school in order to minimise social stigmatisation.

A non-involuting congenital haemangioma is easily excised and the recurrence rate is very low.

5. Cyclophosphamide (C, IV)

Hurvitz et al³⁴ reported a good response to cyclophosphamide in a neonate with diffuse haemangiomatosis, hepatic haemangiomas and cardiac failure, who did not respond to systemic corticosteroids. The major dose-limiting adverse effect is haematologic toxicity, which is usually reversible with discontinuation of therapy. Common adverse effects include nausea, vomiting and reversible alopecia. Adequate hydration and alkalinisation of the urine should

be done to prevent haemorrhagic cystitis and hyperuricaemia. Full blood count, serum uric acid and urine microscopy are monitored regularly during treatment.

Treatment for Special Cases

A. Ulcerated Haemangiomas

Haemangiomas occurring in the anogenital region and on the lips carry a high risk of ulceration. Such ulcerated haemangiomas are often very painful and may bleed or become infected. Depending on their location, they may impair vital functions like feeding, bowel movement or micturition.

1. Conservative management:

- i. Pain relief: oral paracetamol, topical lignocaine (e.g., lignocaine 2% gel with chlorhexidine 0.05%, lignocaine 5% gel). Topical lignocaine must be used sparingly and not more than 3 times per day in the anogenital region to avoid systemic toxicity due to increased absorption in an area of occlusion. EMLA cream should be avoided in young infants as the risk of methaemoglobinaemia is increased.
- ii. Wound care: normal saline wash, bacitracin ointment or zinc oxide paste.
- iii. Hydrocolloid dressing.
- iv. Frequent nappy changes and use of superabsorbent diapers will decrease faecal and urine irritation to ulcerated anogenital haemangioma.
- v. Treat secondary infection, if present, with oral antibiotics e.g., cephalexin, erythromycin empirically until culture results are known.

The following treatment options can be considered in cases not responding to conservative management:

2. Vascular-specific pulse dye laser (B, III).³⁵
3. Systemic corticosteroids (C, IV).

B. Function-impairing Periorbital Haemangiomas

Animal studies have shown that a few days of abnormal visual input in the first few months of life may result in permanent visual defects. For a periorbital haemangioma that obstructs the visual axis or exerts pressure on the globe, immediate intervention is required.

1. Eye patch (C, IV).³⁶

The patient should be referred to and be seen by a paediatric ophthalmologist within 1 to 2 days. Should there be a delay, the unaffected eye should be patched to prevent amblyopia.

2. Systemic corticosteroids (B, III).¹⁶⁻¹⁸
3. Topical corticosteroids (B, III).^{21,22}

Two small case series have shown a decrease in the size of periorbital lesions with topical clobetasol propionate. However, it did not effectively decrease or eliminate anisometropia and hence should not be considered a first-line treatment.

Other Forms of Treatment

Cryotherapy is popular in some countries in Europe and South America, but has not gained much acceptance in the United States due to concerns about potential scarring.^{37,38}

Intralesional bleomycin is not widely used but encouraging results have been reported.³⁹ Compressive wraps have been used successfully for haemangiomas on the extremities.⁴⁰

Conclusion

Medical practitioners should be aware of available therapeutic options, including the use of systemic therapy, for life- or function-threatening haemangiomas. Treatment must be individualised and therapeutic risks weighed against potential benefits. Referral to the relevant specialist should be considered in patients with complicated haemangiomas. Multidisciplinary vascular anomaly clinics need to be established in Singapore as overseas experience has shown that multidisciplinary appraisal by the paediatric dermatologist, paediatrician, paediatric plastic surgeon, paediatric ophthalmologist, wound care nurse and medical counsellor at such clinics are very helpful in the management of complicated haemangiomas.

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