Hemangiomas in the Pediatric Head and Neck: Review and Update

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Grand Rounds Presentation
March 28, 2014

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Overview

- Definitions/Classifications
- Infantile Hemangioma
- Pathophysiology
- Special Circumstances
- Syndromes
- Studies
- Treatment

Fig. 6. Hemangioma in proliferative phase (A) and involution phase (B).
Definitions and Classifications
Vascular Anomaly Classification

- Binary classification system by the International Society for the Study of Vascular Anomalies (ISSVA) in 1996.
- Previous classifications
  - Mulliken and Glowacki (1982)
  - WHO classification

Other Differential Diagnosis
- Infantile myofibromatosis
- Teratoma
- Rhabdomyosarcoma
- Granular cell tumor
- Inflammatory pseudotumor

ISSVA – divides vascular anomalies into binary (2) primary biological categories:
- Vasoproliferative or vascular neoplasms
  - Increased endothelial cell turnover
  - Increased mitotic figures
- Vascular malformations
  - Structural abnormalities of capillary, venous, lymphatic, arterial system
  - Grow in proportion with child

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Infantile Hemangiomas (IH)

- Formal name when people usually refer to a “hemangioma”
- Most common benign tumor in childhood.
- Affects ~1:10 children
- Increased in following populations:
  - Premies
  - Multiple gestational babies
  - In vitro fertilization
  - Caucasians
  - Females
- GLUT-1 positive
- Responds to Propranolol
- Rapid proliferation followed by involution

Fig. 8. Hemangioma in a beard distribution with associated underlying airway hemangioma.
Congenital Hemangiomas

- 2 types
  - Rapidly involuting congenital hemangioma (RICH)
  - Non-involuting congenital hemangiomas (NICH)
- Difficult to distinguish
- GLUT-1 negative
- Medical therapy ineffective for RICH
- NICH may require laser or other surgical therapy
Lobular Capillary Hemangioma

• AKA “pyogenic granuloma”

• Etiology unknown, some evidence shows may be trauma or hormonal influences.

• Higher frequency on anterior nasal septum or anterior aspect of inferior turbinates.

• More common in adults, especially pregnant females.
Kaposiform Hemangioendothelioma & Tufted Angiomas

**Kaposiform Hemangioendothelioma (KHE)**
- Occur anywhere in H&N
- Significant lymphatic component as well as endothelium
- Violaceous cutaneous nodules extending into deep tissue
- Associated with bone resorption leading to localized osteopenia
- Dx with biopsy
- No standard treatment

**Tufted Angiomas (TA)**
- More localized
- No skin involvement
- Dx with biopsy
- No standard treatment
Figure 1997  Kaposiform hemangioendothelioma, clinical and radiographic appearance. A, Cutaneous nodules. B, Deep lesion extending to the skin. C, Coronal computed tomography scan of lesion shown in B.
Infantile Hemangioma (IH) Overview
Diagnosis

- Best diagnosed with thorough history and physical examination.
- Generally not present at birth
- Cutaneous abnormality in form of pallor, duskmess, telangiectasias.
- Bright red macule or papule rash with clear boundaries
- Color may deepen with time
- 5 or more cutaneous hemangiomas
  - Recommend abdominal MRI (Liver)
IH Factoids

- 10-12% white children involved
  - Lower in Asians and blacks
- F:M – ranging 3:2 to 5:1
- Strongly associated with atopy
  - 36% increased risk of AR
  - 67% increased risk of asthma
  - 82% increased risk of eczema
- 2514 cases of 12 yo or younger with ICD-9 code 228.01 showed siblings at relative risk of 2.52, p>0.001.
- 3 families showed linkage and locus heterogenecity to 5q
Fig. 1. Early hemangioma in a newborn.
Phases of Hemangiomas

1. **Proliferative**
   - Begins shortly after birth
   - Continues for up to 1 yr, up to 18 months
   - Reach 85% of size by 5 months of age.
   - May ulcerate

2. **Involutional**
   - Months to years to complete
   - Usually at 6 to 9 months of age
   - Superficial lesions change from bright red to dull red, followed by gray.
     - Flatten and soften
   - Most complete involution by 10 yo
     - Usually imperceptibly scar
     - May have dense fibrofatty tissue or cutaneous telangiectasias

- 75% detected by 4 wk of life
- <5% evident at birth
Figure 199-2. Segmental hemangioma appearance. A, Initial appearance in infancy. B, Late proliferative stage. C, Beginning involutional phase.
Classification of IH

By depth of penetration
- Superficial lesions
  - Upper dermis
  - Strawberry red lesions
- Deep lesions
  - Dermal and subcutaneous tissue
  - Appear darker and more palpable as a mass

By location
- Focal
- Segmental
  - Larger and widespread
Segmental Patterns

1. Frontotemporal
2. Maxillary
3. Mandibular
4. Frontonasal

Fig. 10. 51 segmental facial hemangioma associated with PHACE syndrome.

Diagram of the proposed facial segments.
Pathophysiology

- Aberrant angiogenesis – formation of new blood vessels from preexisting vasculature.

- Aberrant vasculogenesis – formation of new blood vessels from progenitor cells

- Dysregulated differentiation of embryonic cells.
  - Isolated primitive mesenchymal cells CD133+ - human stem and progenitor cells
  - Form GLUT-1 positive vessels within 7-14 days
  - Cells differentiate into endothelium, adipocytes, pericytes.

- Molecular receptor pathways
  - Vascular endothelial growth factor (VEGF)
  - B-adrenergic receptor pathway
  - Glucose transporter 1 (GLUT-1)

- Theories related to some hemangioma-placental connection
Molecular Receptor Pathways

- **Vascular endothelial growth factor (VEGF)**
  - Common mechanism for angiogenesis in tumors
  - Endothelial cells are derived from hemangioma stem cells
    - Produce VEGF-A -> bind to VEGF receptors on these stem cells and stimulate angiogenesis and differentiation into aberrant endothelial cells.
    - In vitro studies – hypoxia and estrogen synergistically enhance hemangioma proliferation.

- **Beta-adrenergic receptor pathway**
  - Propranolol
  - Hypothesis
    - B-adrenergic vasoconstriction -> decreased bulk and flow
      - Ultrasound showed decrease in lesion volume and vessel density after therapy initiation
    - Direct effect on apoptosis in capillary endothelial cells.
      - Down-regulates VEGF-A and HIF-1-alpha -> direct cytotoxic effect in the form of decreased endothelial cell migration and apoptosis.
Molecular Receptor Pathways

Others:

• Angiopoietins
  • ANG-1
  • ANG-2

• Tyrosine protein kinase receptors (Tie2)

• Notch Pathway
  • Notch 1-4
  • Delta-like 1, 3, 4
  • Jagged 1, 2

• Mammalian target of rapamycin complex (mTOR)
GLUT-1

- Glucose transporter 1 (GLUT-1)
  - 97% of Hemangiomas test positive for GLUT-1
  - Normally only in placental blood vessels and blood-brain barrier (BBB) blood vessels
  - GLUT-1 negative Hemangiomas
    - Noninvoluting congenital hemangiomas (NICH)
    - Rapidly involuting congenital hemangiomas (RICH)
    - Do not follow typical clinical course
Histopathology

Proliferative Phase

- Proliferation of immature endothelial cells
  - Alpha-smooth muscle actin positive perivascular cells
- Basal lamina is thickened and multilaminate underneath endothelial cells
  - Forms syncytial masses with lumens
- Light microscopy shows large number of vascular plexus
- Endothelial cells active with hypertrophy and pale staining nucleus
  - GLUT-1 positive
- Nucleus with occasional mitotic figures
- Some mast cells

Picture showing alpha-smooth muscle actin (SMA) – marker for pericytes
Histopathology (cont.)

**Involuting Phase**

- Diminished cellularity
- Flattening of lining endothelial cells
- Relative dilation of vessels
- Progressive deposition of perivascular, intralobular, interlobular fibrous tissue.
- Basement membrane still multilaminate
- High number of mast cells

• High number of mast cells led to hypothesis of them in the regression of IH.
• Picture showing alpha-smooth muscle actin (SMA) – marker for pericytes
Histopathology (cont.)

**Completely Involved**
- “sponge-like” structure
- Scattered thin-walled blood vessels lined with flat endothelial cells
- Basement membrane still multilaminate
- Normal number of mast cells

Picture showing alpha-smooth muscle actin (SMA) – marker for pericytes
Special Locations
Common Complications

- Usually not life-threatening or functionally impairing.

- Cutaneous disfigurement (40-50% resolve incompletely)
  - Telangiectasias
  - Stippled scarring
  - Anectoderma
  - Epidermal atrophy
  - Hypopigmentation
  - Redundant skin with fibrofatty residual tissue

- Psychosocial
  - Negative self image
  - Lack of self confidence

- Vision problems
  - Astigmatic amblyopia - deformation of eye from local compression or periocular tissue distortion
  - Deprivation amblyopia – obstruction of visual axis

- Ulceration
  - Places of repetitive skin trauma – lip, neck
  - Results in scarring

- High-output cardiac failure
  - Large and deep H&N hemangiomas involving parapharyngeal or scalp regions
Figure 199-9. Deep focal hemangioma of infancy, upper eyelid, impinging visual axis.
Upper Airway Hemangioma

• Most common in subglottic region
• Especially high risk with segmental beard distribution
  • Preauricular, chin, lower lip, neck
  • As high as 63%
• Biphasic stridor, exacerbated with agitation, crying, URTI
  • Initially diagnosed as croup
  • Feeding difficulties
  • Sleep disturbances
Subglottic Hemangioma

- Large beard distribution hemangioma + stridor
  - Prompt hospital admission
  - Fiberoptic laryngoscopy
  - Operative endoscopy/bronchoscopy
  - CT neck
    - Reveal focal subglottic lesion or segmental neck lesion with extension into surrounding airway

Fig. 1. (A) A 2-month-old infant with beard distribution hemangioma. (B) Bilateral subglottic involvement in another patient with beard-distribution hemangioma. (C) Tracheal involvement in patient shown in A.
Figure 199-16 Computed tomography (CT) assessment of airway hemangioma of infancy. A and B, CT appearance of focal airway hemangioma of infancy. A, Axial scan; B, coronal scan. Compare endoscopic photograph of the same patient in Figure 199-8B. C and D, CT appearance of segmental airway hemangioma of infancy. C, Sagittal scan; D, axial scan. Compare endoscopic photograph of the same patient in Figure 199-8C.
Figure 2. Subglottic hemangioma. The vocal cords (VC) are identified, and immediately in the subglottis is a red-hued swelling consistent with subglottic hemangiomas (SGH).

Figure 6. Postcricoid venous malformation. (A) At rest. (B) While straining.
Facial Hemangiomas

1. Societal attitudes and recognition of treatment possibilities are changing. Previous lesions allowed to involute are more aggressively treated to prevent unsightly skin changes.

2. Certain areas of face are prone to complications and non-involution, especially midface lesions.

3. Distortion of tissue creating tissue excess and sometimes adjacent bony and soft tissue hypertrophy can cause reconstructive challenges.
Most common pediatric benign parotid gland tumor?

1. Hemangioma
2. Pleomorphic adenoma
3. Mucoepidermoid carcinoma
Parotid Hemangiomas

- Profuse growth
- Disfiguring
- Significant vascular shunting -> high output congestive heart failure
- Facial nerve proximity
Figure 1991. Persistent tissue changes from hemangioma of infancy. A. Fibrotic skin changes from involuted mixed parotid hemangioma of infancy in adult. B. Enlargement of nasal tip from persistent deep focal hemangioma of infancy in adolescent.

Figure 1991.2 Tissue expansion and hypertrophy associated with hemangioma of infancy. A. Focal upper lip hemangioma: Lateral view demonstrating increased lip height and width. B. Mixed parotid-ear hemangioma: Lateral view demonstrating enlargement of lower third of the auricle.
Associated Syndromes

- NOT Kasabach-Merritt Phenomenon
- PHACE Syndrome
Kasabach-Merrit Phenomenon (KMP)

- Described in 1940 by them

- Occurrence of profound thrombocytopenia in association with vascular tumors
  - KHE and TA, not infantile hemangiomas

- Consult hematology/oncology

- Consumptive coagulopathy
  - Thrombocytopenia
  - Hypofibrinogenemia
  - Elevated D-dimers, PT, aPTT

- Requires extensive chemotherapy for risk of bleeding 2/2 thrombocytopenia
  - First line: systemic corticosteroids and vincristine
  - Second line: vincristine, rapamycin, propranolol
  - Others: cyclophosphamide, aspirin,
  - Bleeding: platelet transfusion, cryoprecipitate, FFP, aminocaproic acid.

*Kaposiform Hemangioendothelioma & Tufted Angiomas*
PHACE Syndrome

- First described in 1996 by Frieden et al.
- PHACE Syndrome – neurocutaneous disorder
  - Posterior fossa anomalies
  - Hemangiomas
  - Arterial cerebrovascular abnormalities
  - Coarctation of the aorta/Cardiac abnormalities
  - Eye abnormalities
  - +/- ventral/sternal abnormalities
- Over 300 cases in literature
- Thought to have as high of incidence as Sturge-Weber Syndrome, a neurocutaneous disorder

- Work-up
  - Echocardiogram
  - Brain imaging
  - Formal ophthalmologic evaluation
  - Low threshold for formal airway endoscopy
  - Antiplatelet therapy to prevent stroke
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<td><strong>Possible PHACE Syndrome</strong></td>
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<tr>
<td>Facial Hemangioma &gt;1 cm in diameter PLUS 1 Minor Criteria OR 2 Minor Criteria</td>
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<td>Possible PHACE Syndrome</td>
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<td>Cerebrovascular</td>
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<td>Anomaly of major cerebral arteries</td>
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<td>Persistent embryonic artery other than trigeminal artery</td>
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<td>Arterial stenosis or occlusion with or without moyamoya</td>
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<td>Abnormality or course of the large cerebral arteries</td>
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<td>Persistent trigeminal artery</td>
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*Includes: Haring, looking, tongue thrust, and/or dislocation.
* Includes: Middle cerebral artery, anterior cerebral artery, posterior cerebral artery, or vertebral-basilar system.
* See Structural Brain Anomalies section for discussion.
* Includes: Congenital retinal dysplasia, optic nerve hypoplasia, macular pucker, macular degeneration, or retinal dystrophy.
* Includes: Axial, cerebral, dysplasia, or grey matter heterotopia.
PHACE Syndrome and SGH

• Hemangiomas in this syndrome tend to be larger than 5 cm².
• 98% percent of published PHACE cases report a hemangioma on the face.
• Durr et al. showed that 52% (12 out of 23) of PHACE syndrome patient with large cervicofacial segmental hemangiomas had coexisting subglottic hemangiomas.
  • 6 of these 12 were treated at UCSF
    • 5 female, 1 male
    • 3 Caucasian, 3 Hispanic
    • 1 premature at 36 wks, 5 full term
    • 3 had biphasic stridor, 1 had barking cough, 2 without symptoms
    • Average obstruction of 50%
Studies
Labs
Radiology

Fig. 1. Hemangioma. a: Pedal US with power Doppler at 30 weeks' gestation reveals a very vascular scalp mass. b: Sagittal short-T2-weighted coronal MRI in the same patient shows the mass (arrow), which is isointense to white matter and contains cystic areas (arrowheads) caused by prior vascular insult. c: Axial contrast-enhanced CT in a 3-month-old boy demonstrates an intensely enhancing, sharply demarcated and lobulated parotid hemangioma (arrow). d: Axial contrast-enhanced CT in a 6-year-old girl with an involving hemangioma shows faintly enhancing residual hemangioma (arrow) with interspersed fibrotic tissue (arrowhead). e: Axial T2-W STIR MRI image in a 4-month-old girl demonstrates a partial hemangioma (arrow) that is isointense with active central nodules. Prominent high-flow vascular flow voids are seen. f: Axial gadolinium-enhanced T1-weighted SSFP image in the same patient. (arrow) Demonstrates intense enhancement.
Laboratory Tests

- GLUT-1
- Lewis Antigen (LeY)
- Merosin
- Urinary basic fibroblast growth factor (bFGF) level
  - Distinguish SGH from vascular or lymphatic malformation
  - Mast cells produce bFGF
  - Serial urinary BFGF levels may follow response to any treatment
- Mostly research only
  - Proliferating cell nuclear antigen
  - Vascular endothelial growth factor
  - Type IV collagenase
  - Urokinase
Radiology

- Ultrasound
  - Non-specific echogenic mass
  - Dubois et al set 5 vessels per cm² and Doppler frequency shifts greater than 2 kHz as criteria in proliferative phase.
    - Prospective in 116 patients showed 84% sensitivity and 98% specificity.
Radiology

- Magnetic resonance imaging (MRI) with gadolinium is study of choice.
  - Well circumscribed, lobulated mass
  - Salt and pepper pattern
  - Dilated feeding and draining vessels
  - Proliferative phase
    - Appears solid and intermediately intense on T1-spin echo images
    - Hyperintense with flow voids on T2-weighted images.
  - Involuting phase
    - Nonenhancing or variably enhancing with variable fat content

B – axial T1-weighted MRI – well defined mass, isoechoic to muscle
C – coronal fat-saturated MRI of neck shows high intensity to muscle with flow voids (arrows).

Involuting phase of mandibular IH on 2 yo boy who received laser treatment.
Axial T1-weighted MRI – mass with loose fibrofatty tissue.
Radiology

• Computed Tomography (CT)
  • Homogenous masses with intense persistent enhancement
  • Bony involvement
  • Detecting phleboliths, characteristic of venous and lymphatic venous malformations.

Figure 100-3. Vascular anomaly imaging: A, Three-dimensional CT angiography (A1) and coronal CT scan (A2) of deep hemangoma of infancy. B, Three-dimensional CT angiography and coronal CT scan of venous malformation. C, Three-dimensional CT angiography and coronal CT scan of lymphatic malformation.
Treatment

- No “gold standard”
- Active nonintervention
- Pharmacological
- Surgical
Treatment Principles

• Small isolated or multiple skin lesions on the face found soon after birth should be treated as soon as possible in order to prevent its progress into the proliferative phase

• Close observation for involuting hemangiomas.

• Factors:
  • Size, stage, location, presence of ulceration, cosmetic considerations, functional compromise, psychosocial implications.
  • Interference with visual axis (eyelid)
  • Risk to cartilage: ear or nose
  • Airway compromise
  • Feeding difficulties
Watchful Waiting

- Small, stable in non-vital areas
- Observe, record, photography
- Intervention with:
  - Accelerated growth
  - Hemorrhage
  - Infection
  - Ulceration
  - Functional problems:
    - Dysphagia
    - Trouble breathing
    - Vision problems
    - Hearing problems
- Leads to high output congestive heart failure
- Involves: eyelids, nose, lips, auricle
Pharmacologic Treatment

- Corticosteroids
- Interferon alpha-2a
- Imiquimod
- Anti-cancer drugs
  - Cyclophosphamide
  - Vincristine
  - Bleomycin
- Becaplermin, recombinant platelet-derived growth factor, 0.01% gel for ulcerations
- Propranolol
Corticosteroids

- **Historical treatment** (>30 yrs) of choice for subglottic and parotid lesions
- Effective during proliferative phase and can slow or cease growth.
- Prednisolone 2 to 5 mg/kg/d for 4-10 wks
- Dose is tapered off
- Up to 90% response rate
- High morbidity
  - Behavioral changes, hypertension, immunosuppression, gastrointestinal irritation, adrenal insufficiency, cushingoid facies
  - Inhibition of hypothalamic-pituitary-adrenal axis
- Can be injected intralesionally
  - Be aware of particle embolization -> blindness
Interferon alpha-2a

- Anti-angiogenic activity
  - Can be used in proliferative or involutional stage
- Subcutaneous single daily dose over several months (<3 mo)
- 3 million U/m2
- Monitor CBC, LFT, Coags
- 80-90% response rate
- Common complications
  - Flu-like symptoms, somnolence, anorexia, diarrhea, constipation, neutropenia, elevated LFTs
- Pertinent complication – epilepsy, spastic diplegia, lower limb disability

Spastic diplegia's particular type of brain damage inhibits the proper development of upper motor neuron function, impacting the motor cortex, the basal ganglia and the corticospinal tract. Nerve receptors in the spine leading to affected muscles become unable to properly absorb gamma amino butyric acid (GABA), the amino acid that regulates muscle tone in humans. Without GABA absorption to those particular nerve rootlets (usually centred, in this case, around the sectors L1-S1 and L2-S2), affected nerves (here, the ones controlling the legs) perpetually fire the message for their corresponding muscles to permanently, rigidly contract, and the muscles become permanently hypertonic (spastic).
Imiquimod

- Imidazole quinolone amine immunomodulatory drug
- Used for herpes, BCC, SCCis, actinic keratosis, lentigo maligna
- Martinez in 2002 attempted to apply this topically in 5% cream every other day and achieved ideal efficacy.
- Mechanism may be by enhancing immunity through cytokines including: interferon-alpha, IL-6, TNF-alpha
- Sunamura found inhibiting tumor growth and anti-angiogenesis effect of IL-12 may play a role
- Qiu showed a 4% rate of severe local reactions including disfiguring depigmented scars.
- Mao showed 78.9% of patients with IH had site itching, erythema/edema, peeling, erosion, crusting, ulceration, scarring. 4/19 had fever, nausea or diarrhea.
Radiation Therapy

- Gamma ray produced by radioisotope to bombard nuclei area leading to cell death.
- 2 Gy per dose for total of 10 Gy maximum
- Radioisotope therapy with strontium-90 used.
- Potential cancer formation
Leaute-Labreze et al discovered Propranolol

2 patient with large segmental cervicofacial hemangiomas were treated with propranolol when symptoms of high output cardiac failure occurred. Noted rapid and dramatic regression of the cutaneous lesions as well

The underlying problem in high output failure is a decrease in the systemic vascular resistance that threatens the arterial blood pressure and causes activation of neurohormones, resulting in an increase in salt and water retention by the kidney.
A – 9 wks of age, already received 4 wk of steroid

B – 10 wks of age, 1 wk of propranolol – now able to spontaneously open eye

C – 6 mos of age, ~4 mo of propranolol, steroids d/c at 2 mo

D – 9 mos of age, propranolol d/c now

Figure 1 (facing page). Photographs of Patient 2 before and after Treatment with Propranolol. Panel A shows the patient at 9 weeks of age, before treatment with propranolol, after 4 weeks of receiving systemic corticosteroids (at a dose of 3 mg per kilogram of body weight per day for 2 weeks and at a dose of 5 mg per kilogram per day for 2 weeks). Panel B shows the patient at 10 weeks of age, 7 days after the initiation of propranolol treatment at a dose of 2 mg per kilogram per day while prednisolone treatment was tapered to 3 mg per kilogram per day. Spontaneous opening of the eye was possible because of a reduction in the size of the subcutaneous component of the hemangioma. Panel C shows the patient at 6 months of age, while he was still receiving 2 mg of propranolol per kilogram per day. Systemic corticosteroids had been discontinued at 2 months of age. No subcutaneous component of the hemangioma was noted, and the cutaneous component had considerably faded. The child had no visual impairment. Panel D shows the child at 9 months of age. The hemangioma had continued to improve, and the propranolol treatment was discontinued.
Propranolol: Mechanism of Action

• Synthetic, beta-adrenergic receptor-blocking agent.

• Nonselective: blocks both beta-1 and beta-2 adrenergic receptors.

• Results in decrease in HR and BP by:
  • Chronotropic, inotropic, vasodilator responses decrease when beta-receptors blocked
  • Inhibits renin release by kidneys
  • Decreases sympathetic tone.

• Undergoes first pass metabolism by liver with only ~25% of the oral propranolol reaching systemic circulation.

<table>
<thead>
<tr>
<th>TABLE 1 Drug Interactions</th>
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</thead>
<tbody>
<tr>
<td><strong>Increase Blood Levels/Toxicity</strong></td>
</tr>
<tr>
<td>Inhibitors of CYP2D6.</td>
</tr>
<tr>
<td>Amiodarone, cimetidine (but not ranitidine), delavudin, fluoxetine, paroxetine, quinidine, and ritonavir</td>
</tr>
<tr>
<td>Inhibitors of CYP1A2.</td>
</tr>
<tr>
<td>Imipramine, cimetidine, ciprofloxacin, fluvoxamine, isoniazid, ritonavir, theophylline, zileuton, zolmitriptan, and rizatriptan</td>
</tr>
</tbody>
</table>
Propranolol

• Proposed theory for infantile hemangioma treatment:
  • Vasoconstriction, decreased renin production, inhibition of angiogenesis, stimulation of apoptosis... unknown.
  • Thaivalappil et al. showed significant decrease in urinary MMP-9 in patients treated with propranolol vs untreated pts with IH.

• Used to treat: cardiac arrhythmias, angina, hypertension, hypertrophic cardiomyopathy, outflow obstruction in CHF.

• Still investigational
  • No FDA approved indication in pediatric patients
  • Consent for off-label use

Thaivalappil – measured 1000+ urinary proteins in 3 steroid, 3 pro, 5 controls (untreated IH)
Propranolol Complications

- Bradycardia
- Hypotension
- Bronchospasm
- Hypoglycemia
- Hyperkalemia
- Gastrointestinal discomfort
  - Diarrhea
  - GERD
- Sleeping Problems
  - Hypersomnolence
  - Night terrors

- From consensus statement
- Hypoglycemia MOA – beta2 receptors stimulate hepatic glycogen breakdown, glycogenolysis and pancreatic release of glucagon.
- Hyperkalemia – inhibit renin release so decrease aldosterone so -> hyponatremia and hyperkalemia.
- Tx of RAD/asthma is albuterol – beta 2 agonist -> use ipratropium for bronchospasm. (anticholinergic)
- Tx of beta blocker overdose is Glucagon
### Table 3
Patients with theoretical increased risk of adverse effects from propranolol for infantile hemangioma

<table>
<thead>
<tr>
<th>Population</th>
<th>Side Effect</th>
<th>Reason for Concern</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1 year of age, particularly LBW infants</td>
<td>Hypoglycemia</td>
<td>Limited glycogen stores, inability to communicate symptoms</td>
</tr>
<tr>
<td>Patients previously treated with systemic steroids</td>
<td>Hypoglycemia</td>
<td>Muted counter-regulatory cortisol response secondary to adrenal suppression</td>
</tr>
<tr>
<td>PHACE syndrome patients with cerebrovascular anomalies</td>
<td>Hypoperfusion of brain</td>
<td>Narrowed, stenotic vessels may require higher blood pressure for perfusion; propranolol associated with decreased cerebral blood flow</td>
</tr>
<tr>
<td>PHACE syndrome patients with aortic arch obstruction</td>
<td>Systemic hypoperfusion</td>
<td>Aortic obstruction may require higher blood pressure to maintain perfusion to segments distal to the obstruction</td>
</tr>
<tr>
<td>Hemangioma-related high-output cardiac failure (ie, large liver hemangioma)</td>
<td>Decompensation of heart failure</td>
<td>Decreased heart rate/contractility limits cardiac response to high-output demands</td>
</tr>
</tbody>
</table>

Abbreviation: LBW, low-birth weight.
Propranolol Randomized Control Trial

- Hogeling et al. conducted double blind RCT of propranolol vs. placebo.
- 40 kids ages 9 wk to 5 yr with
- 2 mg/kg/day divided TID of oral propranolol vs. oral placebo solution for 6 mo.
- Measured volume estimation using serial hemispheric measurements of tumor.

- Started with 1 mg/kg/day for 1 wk then increased.
- Consult with pediatric cardiology – screen with BP, HR, EKG, echo, CBC, BMP, LFT, glucose
- Measured at 0, 4, 8, 12, 16, 20, 24 wk

**FIGURE 1**
Trial participants flow diagram.
Propranolol safely treated IH in his heterogeneous group of patients.

P values were significant with small number of patients.
**Figure 3**
Six-month-old girl with deep periorbital IH responding to propranolol at weeks 0 (A), 12 (B), and 24 (C).

**Figure 4**
Four-month-old boy with a nasal tip IH treated with propranolol at weeks 0 (A), 12 (B), and 24 (C).

**Figure 5**
Twelve-month-old girl with a nasal tip IH involution with propranolol at weeks 0 (A), 12 (B), and 24 (C).

**Figure 6**
Five-month-old girl with minimal response of IH on left eyebrow to propranolol at weeks 0 (A), 12 (B), and 24 (C).
Propranolol vs. Steroid vs. Both

• Malik et al. conducted prospective study comparing propranolol vs. prednisolone vs. both in potentially disfiguring or functionally threatening IH.

• 30 patients aged 1 wk to 8 mo randomized into 3 groups.

• Dimensions, color, consistency, photo based on VAS.

• 75% with no regrowth up to 1 mo of Tx cessation = Success
Results

• Mean initial response time (days) [Mean initial response time and consistency change not well defined].
  • A – 4.1 +/- 3.3 SD
  • B – 9.78 +/- 7.8 SD
  • C – 4.7 +/- 3.4 SD

• Consistency change
  • Very early in A (24 hr) compared to B and C (8 days)

• VAS results [Visual Analog Scale: -10 to +10]
  • Color fading – A (<48hr) compared to B and C
  • Flattening – A and C more than B
  • Mean Reduction in Size – A and C at 3, 6, 12, 18 mo; B only at 6 mo.

• Complications [multiple in a patient with steroids]
  • A – 2 w/ complications: 1 hypoglycemia, 1 somnolence
  • B – 9 w/ complications: 5 Cushingoid appearance, 3 GI upset, 3 regrowth during holiday
  • C – 7 w/ complications: 6 Cushingoid appearance, 4 GI upset, 1 regrowth, 1 infection
Multidisciplinary Strategy

- Retrospective review of 49 patients with infantile hemangioma involving otolaryngology, cardiology, dermatology by Cushing et al. in Seattle.
  - Carvedilol had trial for outpatient initiation in the past.
  - Outpatient initiation of propranolol therapy.
  - Target dose of 2 to 3 mg/kg/d divided TID.
  - Recorded BP 1, 2, 3 hrs post-administration.
  - Families received standard instructions for home HR, S/E, fasting.
  - Baseline H&P, EKG with possible TTE, MRA head.
  - Exclusion criteria ->

<table>
<thead>
<tr>
<th>Table 1. Exclusion Criteria for Propranolol Therapy in Hemangioma</th>
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<tbody>
<tr>
<td>Exclusion Criterion</td>
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<tr>
<td>----------------------------------</td>
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<tr>
<td>Known hypersensitivity to propranolol</td>
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<tr>
<td>Untreated heart failure</td>
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<tr>
<td>&gt;First-degree AV block</td>
</tr>
<tr>
<td>Resting heart &lt;2 SD of normal</td>
</tr>
<tr>
<td>Resting blood pressure &lt;2 SD of normal</td>
</tr>
<tr>
<td>Wolff-Parkinson-White syndrome</td>
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<tr>
<td>History of unexplained syncope</td>
</tr>
<tr>
<td>Bronchial asthma</td>
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<tr>
<td>History of impaired renal or liver function</td>
</tr>
<tr>
<td>Less than 1 week of age or expected to have long periods of fasting</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
</tr>
</tbody>
</table>
Multidisciplinary Strategy

- Hemangioma requiring treatment
  - Cardiology Consultation
    - Screen
      - Exclusion Criteria?
      - Inpatient vs Outpatient
      - EKG
      - Need ECHO
    - Risk discussion with family
    - Calculate dosing
      - 0.5-0.7 mg/kg/dose tid
      - total daily dose = 2-3 mg/kg/day divided tid

- Monitor HR, SBP, DBP hourly for 3 hours post dosing
  - Teach
    - Home HR monitoring x 1 week
    - “Fast” prevention
  - Provide contact information
  - Follow up in 1 month for dose adjustment
Multidisciplinary Strategy

- Total of 49 patients
- Mean age at initiation 5.8 +/- 8.4 mo.
- Female:Male 35:9
- 33 involved head and neck, 3 in airway
- 5 patients underwent inpatient therapy
  - 3 had airway compromise, 1 had early heart failure/arrhythmia, 1 social concerns
- HR, SBP, DBP were measured and z scores calculated
  - HR – no changes in z score greater than 2 from baseline
  - SBP and DBP – significant changes at only 2 hrs for both absolute and z scores from baseline
- Conclusion
  - Outpatient initiation of propranolol for hemangioma is safe with a multidisciplinary approach with someone experienced with pediatric propranolol therapy.
Propranolol Consensus Statement

• Consensus conference held on Dec 9, 2011

• When to treat: all individualized

• Contraindications
  • Reactive airway disease/Asthma
  • Significant cardiac disease (cardiogenic shock, heart failure, sinus bradycardia, 2nd or 3rd degree heart block or greater, hypotension).
  • Meta-analysis of 154 patients showed adverse event rate of 18%.
  • Hypersensitivity to propranolol hydrochloride.

• Consult cardiology
  • Baseline EKG for bradycardia, arrhythmia, famhx of arrhythmia or maternal connective tissue disease.
  • Echocardiogram for suspected cardiac/aortic arch anomalies.

• PHACE Syndrome
  • All large facial hemangiom as -> MRI/MRA of head/neck/chest

Consensus was not achieved on the use of ECG for all children with IH, but ECG should be part of the pre-treatment evaluation in any child when
1. the HR is below normal for age113: newborns (.1 month old), .70 beats per minute, infants (1–12 months old), 80 beats per minute, and children (.12 months old): .70 beats per minute.
2. there is family history of congenital heart conditions or arrhythmias (eg, heart block, long QT syndrome, sudden death), or maternal history of connective tissue disease.
3. there is history of an arrhythmia or an arrhythmia is auscultated during examination.
A) Inpatient Initiation of Propranolol: Suggested for infants < 3 weeks of gestationally corrected age or with co-morbid conditions

- Initiate propranolol 0.33 mg/kg po q6 hrs (1mg/kg/day)
  - Check BP and HR at 1 and 2 hrs after first dose
  - Not Tolerated
  - Tolerated
  - Increase dose to 0.66 mg/kg po q6 hrs
    - Check BP and HR at 1 and 2 hrs after first 1-3 doses
  - Not Tolerated
  - Tolerated
  - Prepare for discharge, counsel parents to:
    1. Ensure minimum of 6 hrs between doses
    2. Recognize signs of hypotension, bradycardia, and hypoglycemia
    3. Feed regularly and hold medication if po intake compromised
    - Discharge to home

B) Outpatient Initiation of Propranolol: Suggested for infants > 8 weeks of gestationally corrected age and adequate social support.

- Initiate propranolol 0.33 mg/kg po q6 hrs (1mg/kg/day)
  - Tolerated
  - Tolerated for 3-7 days
  - Increase dose to 0.5 mg/kg po q6 hrs
    - Tolerated for 3-7 days
  - Tolerated
    - Consider keeping at 1mg/kg/day and assess dose efficacy
    - Discharge home

FIGURE 1
(A) Summary of recommended dose initiation for inpatient scenario. (B) Summary of recommended dose initiation for outpatient scenario. PO, oral ad ministration; q6h, every 6; q8h, every 8.
Propranolol Consensus Statement

- **Target dose**- 2 mg/kg/day divided in 3 doses with a range from 1 and 3 mg/kg/day

- **Outpatient Titration** - Infants and toddlers older than 8 wks gestation age without significant comorbid conditions.

- **Monitor HR & BP**
  - 1 set of vitals 1 and 2 hr after initiation or significant dose increase
  - Bradycardia (established criteria)
    - Newborns (<1 mo old) <70 bpm
    - Infants (1-12 mo old) <80 bpm
    - Children (>12 mo old) <70 bpm
  - Hypotension (systolic BP but not as established)
    - Newborns (<1 mo old) <57 mmHg (<5th percentile oscillometric) or <64 mmHg (2 SD auscultation)
    - Infants (1-12 mo old) <85 mmHg (<5th percentile oscillometric) or <65 mmHg (2 SD auscultation)
    - Children (>12 mo old) <88 mmHg (<5th percentile oscillometric) or <66 mmHg (2 SD auscultation)

- **Make sure to feed at least q4hr**
  - No routine screening for serum glucose recommended.

- **Discontinue of concurrent illness**, especially in setting or decreased oral intake.
Propranolol and SGH IH

- Fuchsmann et al. showed effect in 7 patients retrospectively
  - 4 patients resulted in regression and disappearance of dyspnea, ability to feed orally in 1 wk, and discharge home after 10 days.
    - Endoscopy in 5 wks showed 80% regression of lesions (pic on next slide)
  - 3 patients had concomitant steroids.
  - 1 child already had undergone laser debulking, local steroid injections and systemic steroids, all ineffective
Figure 1. Endoscopic assessment of 2 patients with subglottic hemangiomas. A and B, Initial views. C and D, One month after starting propranolol (patients were treated only with propranolol and 7 days of prednisone [1 mg/kg]).

Figure 2. Two-month-old patient with a hemifacial cutaneous hemangioma. A, Initial view. B, Improvement after 2 months of propranolol treatment. C, Further improvement after 9 months of treatment.
GOSH Guidelines for SGH

Bajaj et al. at Great Ormond Street Hospital came up with guidelines for treatment with propranolol for laryngotracheobronchoscopy confirmed isolated subglottic hemangiomas.

<table>
<thead>
<tr>
<th>Pre-treatment investigations</th>
</tr>
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<tbody>
<tr>
<td>Detailed history &amp; examination</td>
</tr>
<tr>
<td>Blood tests (FBC, U&amp;E, LFT, glucose, TFT)</td>
</tr>
<tr>
<td>ECG, ECHO</td>
</tr>
</tbody>
</table>

Treatment

- Baseline pulse, BP
- Start propranolol 1 mg/kg/day in 3 divided doses
- Increase to 2 mg/kg/day 1 week later
- Check pulse BP every 30 min for first 2 hours on starting & changing treatment
- Weekly BP check for duration of treatment

Follow up

- Response to propranolol assessed at 6 weeks endoscopy
- Repeat endoscopies at 3-monthly intervals
- Wean from propranolol after 12 months depending on response

- Unilateral smooth swelling in the subglottis
- Wean – half dose for 2 wks, then half again for next 2 wk.
1 – 7 wk old with zone 2 lateral cheek IH. 5 wk of Tx.
Decrease tumor vol 1.2 cc -> 4.9 cc

2 – 4 wk old with deep parotid IH zone 3. after 23 wk of Tx

3 – 12 wk old with deep parotid IH. 33 wk of Tx.
Surgical Options

- Tracheostomy
- Cryotherapy
- Laser therapy
- Excision
ABC’s

• Airway management for airway IH.
• Tracheostomy to bypass subglottis.
Cryotherapy

- Used in 1960s
- Liquid nitrogen

- Cellular damage during freezing
  - Intra and extracellular icy crystals form mechanically breaking cellular membrane.

- Complications:
  - Cold urticarial
  - Cryoprecipitate fibrinogen
  - Cryoglobulinemia
  - Proliferative or atrophic scarring
  - Hyperpigmentation or hypopigmentation
  - Milia
  - Tissue contracture
Laser Therapy

- Argon Laser
- Pulsed Dye Laser
- Nd:YAG Laser
- KTP Laser

Indicated for:
- Early, superficial hemangiomas
- Superficial portion of compound hemangiomas

Repeated at 2-4 wk intervals

Choice of laser based on location, size, depth
Argon Laser

- Short wavelength of 488-514 nm
- Unselective thermal damage of blood vessels
- Easy to damage adjacent normal tissue -> scarring/pigmentation
  - 40% treated with Argon Laser may be accompanied by hypertrophic scarring
  - Limited use
Flash Lamp-pumped Pulsed Dye Laser (FPDL)

- Wavelength of 585 or 595 nm Destroys blood vessels selectively
- Photocoagulation of targeted vessels, keeps overlying skin intact
- Promote regression and inhibit endothelial cell proliferation

Settings:
- Pulse duration of 300-450 microseconds
- Spot size of 2-10 mm
- Energy density of 3-10 J/cm²

Treated area turns off-white with surrounding erythema which resolves 7-14 days
- Smear area with panthenol ointment
- Cleanse area with povidone-iodine solution
- Repeat in 4 wks if necessary

Common side effects:
- Atrophic scars
- Ulcerations
- Postoperative purpura
- Transient hyperpigmentation

The laser beam is overlapping and the skin is protected through the cooling system. The energy needs to be decreased in some sensitive areas (e.g. infraorbital skin), as well as easily remodeled areas (e.g. neck and prothorax). Through adjusted wavelengths (585, 590, 595 or 600 nm), prolonged pulse duration (1.5~40 ms) with large spot size and energy of 5~5 J/cm², the depth of penetration is deeper and the damage remains within the blood vessels.
Figure 199.15  Laser treatment of superficial hemangioma. A. Pretreatment appearance. B. Appearance after three pulsed dye laser treatments.

Figure 199.10  Hemangioma of infancy, lip. A. Ulcerated hemangioma during proliferation. B. Lip appearance after several pulsed dye laser treatments and ulcer healing.
Nd:YAG

- Neodymium:yttrium aluminum garnet is a solid laser emitting continuous or pulse type wave of infrared and invisible light
- Wavelength of 1064 nm and penetration depth of 4-6 mm
- May be utilized for deep hemangiomas
- Very painful so performed under general anesthesia
- 1-4 days after treatment, will remain swollen with possible blister/scab
- Wound heals 2-4 weeks post-treatment
- Repeated at 5-8 intervals
- Suitable for larger and up to 2 cm deep hemangiomas
KTP Laser

- Potassium titanyl phosphate crystal modifying a 1064 nm Nd:YAG
- Solid state laser
- Wavelength of 532 nm.
  - Similar to hemoglobin absorption peak
  - Incidence of postoperative purpura decreases greatly
- Penetration of KTP laser is weaker
- Epidermal melanin also can be targeted leading to pigmentation disturbances
CO2 Laser

- Removes superficial blood vessels
- Rarely used due to high rate of scar formation and poor effects
Surgical Treatments

• Focal cutaneous lesions
  • Standard elliptical excision
  • Along natural relaxed skin tension lines

• Subglottic hemangiomas
  • Tracheostomy to secure airway
  • Endoscopic laser surgery
    • Carbon dioxide laser – high rates of recurrence, may lead to stenosis
    • Nd:YAG
    • Argon laser
  • Microdebrider
  • Transcervical laryngofissure approach
    • Inferior thyroid cartilage divided and excised submucosally
    • Reapproximated with interpositional cartilage graft (thyroid donor)
    • Patient left intubated for days
Fig. 3 (a) One-year-old male with proliferating right cheek hemangioma despite one course of systemic steroids. (b) Post-excision. Some areas of cutaneous involvement were purposely left in order to close the wound without tension. Future additional laser will be performed in the future if the skin redness persists.

Fig. 4 Combined laser and surgical treatment of large nasal tip mixed nodular hemangioma of infancy. A, Before treatment. B, After residual deep hemangioma excision via external rhinoplasty approach.
Figure 19914. Combined laser and surgical treatment of large upper lip-cheek mixed segmental hemangioma of infancy. A, Before treatment. B, After laser treatment and deep hemangioma excision.
Conclusion

• Infantile hemangiomas are the most common benign tumor in the pediatric head and neck, including parotid masses.
  • Distinguish between other vascular tumors and malformations

• Most do not require active treatment with a predictable proliferation and involution phase.

• When IHs impinge on vital organs or affect aesthetics, treatment will be necessary.
  • Large segmental head and neck hemangiomas have a high concurrence of an airway, particularly subglottic, hemangioma.

• Propranolol, although mechanisms unknown, has become the mainstay treatment for IH over corticosteroids and other pharmacologic therapies.
  • Requires multi-disciplinary approach for the best individualized management of the patient.
Board Review

- Infantile hemangiomas
  - GLUT-1 positive
  - Most common pediatric parotid mass
  - PHACE Syndrome association
    - NOT Kasabach-Merritt Phenomenon
  - Therapy with Propranolol
References


References (cont.)


