Conflict of Interest

- I have no financial relationships to disclose
- I will discuss the following off label use and/or investigational use in my presentation:
  - Topical timolol maleate for treatment of infantile hemangiomas
Photographs

- Patients – with consent
- Published literature
Objectives

• To review the natural history of infantile hemangiomas
• To examine recent advances in the treatment of infantile hemangiomas
• To discuss when and how to treat infantile hemangiomas
Case 1: Infant girl (1 month)
Case 1: Infant girl (2 months)
Case 2: Infant girl (4 months)
Case 3: Infant girl (birth)
Case 3: Infant girl (5 months)
Case 4: Infant girl (2 months)
Case 5: Infant boy (4 months adjusted age)
Part I:  Natural History
Biology

• Most common benign vascular tumor of infants
  – 4.5% of all infants (up to 10% of Caucasian infants)

• Predominantly cutaneous
  – Also mucosal, visceral

• Present soon or after birth
  – “Vascular stain,” “bruise,” “discoloration”

• Growth starts within a few weeks

• Typical growth phase, plateau, involution

• Residual scarring, discoloration, deformity

• Functional deficits

# 2014 ISSVA Classification

## 2014 ISSVA classification (condensed)

<table>
<thead>
<tr>
<th>Vascular tumors</th>
<th>Benign</th>
<th>Locally aggressive/borderline</th>
<th>Malignant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infantile hemangiomas</td>
<td></td>
<td>Kaposiform hemangioendothelioma</td>
<td>Angiosarcoma</td>
</tr>
<tr>
<td>Congenital hemangiomas</td>
<td></td>
<td>Retiform hemangioendothelioma</td>
<td>Epithelioid hemangioendothelioma</td>
</tr>
<tr>
<td>(including RICH, NICH, PICH)</td>
<td></td>
<td>Kaposi sarcoma</td>
<td>Others</td>
</tr>
<tr>
<td>Tufted angioma</td>
<td></td>
<td>Others</td>
<td>Others</td>
</tr>
<tr>
<td>Spindle cell hemangioma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epithelioid hemangioma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Vascular malformations</th>
<th>Simple</th>
<th>Combined</th>
<th>Associated with other anomalies</th>
</tr>
</thead>
<tbody>
<tr>
<td>CM</td>
<td>CM + VM</td>
<td></td>
<td>Klippel-Trenaunay syndrome</td>
</tr>
<tr>
<td>LM</td>
<td>CM + LM</td>
<td></td>
<td>Parkes-Weber syndrome</td>
</tr>
<tr>
<td>VM</td>
<td>CM + AVM</td>
<td></td>
<td>Servelle-Martorell syndrome</td>
</tr>
<tr>
<td>AVM</td>
<td>LM + VM</td>
<td></td>
<td>Sturge-Weber syndrome</td>
</tr>
<tr>
<td>Arteriovenous fistula</td>
<td>CM + LM + AVM</td>
<td></td>
<td>Maffucci syndrome</td>
</tr>
<tr>
<td>Telangiectasia</td>
<td>Others</td>
<td></td>
<td>Others</td>
</tr>
<tr>
<td>Others</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Prospective Study of Infantile Hemangiomas: Demographic, Prenatal, and Perinatal Characteristics

The Hemangioma Investigator Group: Anita N. Haggstrom, MD, Beth A. Drolet, MD, Eulalia Baselga, MD, Sarah L. Chamlins, MD, Maria C. Garzon, MD, Kimberly A. Hori, MD, Anne W. Lucky, MD, Anthony J. Mancini, MD, Denise W. Metry, MD, Brandon Newell, MD, Amy J. Nopper, MD, and Ilona J. Frieden, MD
Epidemiology

- Infants with hemangiomas were more likely to be:
  - Female
  - White, non-Hispanic
  - Premature
  - Product of multiple gestation

- Mothers of infants with hemangiomas were more likely to have:
  - Older maternal age
  - Preeclampsia
  - Placenta previa

*J Pediatr* 2007; 150:291-4
Low Birth Weight

- Strongest predictive factor

* There were only 3 infants in the control group in this category

Genetics

• Gene Associations
  – *KDR (VEGFR2)*
  – *FLT4 (VEGFR3)*
  – Others

• Twin Study
  – 202 sets of twins (22% monozygotic)
  – No significant difference of incidence between mono- and dizygotic twins
  – Risk factors birth weight, gestational age, gender

*J Pediatr Hematol Oncol* 2014; 36:587-93

*Pediatr Dermatol* 2016; 33:178-83
Growth Characteristics

Pediatrics 2008;122:360–367
Growth Characteristics

- Early Prolif (3.2 ± 1.7 mo): 80%
- Late Prolif (6.2 ± 2.5 mo): 93%
- Involuting (11 ± 4.1 mo): 100%

*Pediatrics* 2008;122:360–367
Classification of Hemangiomas According to Growth Phase of the Lesion (Stage), Clinical Morphology (Morphologic Subtype), and Depth of Skin/Soft Tissue Involvement (Description)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Morphologic Subtype</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nascent</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early proliferative</td>
<td>Localized</td>
<td>Superficial</td>
</tr>
<tr>
<td>Late proliferative</td>
<td>Segmental</td>
<td>Deep</td>
</tr>
<tr>
<td>Plateau</td>
<td>Indeterminate</td>
<td>Mixed</td>
</tr>
<tr>
<td>Involuting</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abortive</td>
<td></td>
<td>(Terminated Growth)</td>
</tr>
</tbody>
</table>

*Pediatrics* 2008;122:360–367
Superficial
Superficial
Superficial
Mixed
Mixed
Mixed
Deep
Deep
Segmental
Segmental
Subglottic

Otolaryngol Clin N Am 2008; 41:903-11
Multiple Hemangiomatosis
PHACE(S) Syndrome

- Posterior fossa malformations
- Hemangioma
- Arterial anomalies
- Cardiac anomalies / aortic coarctation
- Eye abnormalities
- Sternal clefting / supraumbilical raphe

Pediatrics 2009; 124:1447-56
PHACE(S) Syndrome
PHACE(S) Syndrome
Other Hemangioma Syndromes

- **LUMBAR**
  - Lower body / Lumbosacral hemangioma
  - Urogenital defects
  - Myelopathy
  - Bony deformities
  - Anorectal malformations, arterial anomalies
  - Renal anomalies

- **PELVIS**
  - Perineal hemangioma
  - External genitalia malformations
  - Lipomyelomeningocele
  - Vesicorenal abnormalities
  - Imperforate anus
  - Skin tag

*Arch Dermatol* 2006; 142:884-8

*J Pediatr* 2010; 157:795-801
Congenital Hemangiomas
Congenital Hemangiomas
Congenital Hemangiomas

- RICH – Rapidly involuting congenital hemangioma
- NICH – Non-involuting congenital hemangioma
- PICH – Partially involuting congenital hemangioma
Part II: Treatment
Traditional Therapy

- **Surgical Excision**
  - Proliferative stage or later

- **Corticosteroids**
  - Intralesional injection
  - Systemic

- **Systemic Chemotherapy**
  - Vincristine / Vinblastine

- **Laser**
  - Vascular (i.e. pulsed dye)
  - Ablative (CO2, Nd-YAG)
Propranolol for Severe Hemangiomas of Infancy


TO THE EDITOR: Despite their self-limited course, infantile capillary hemangiomas can impair vital or sensory functions or cause disfigurement. Corticosteroids are the first line of treatment for problematic infantile capillary hemangiomas¹,²; other options include interferon alfa³ and vincristine.¹ We have observed that propranolol can
Treatment Advances
Propranolol

- Non-selective beta-blocker
- Previously used predominantly for cardiovascular indications in infants
- Cheap
- Oral formulation available
- Oral dosing (TID>>BID)

*Pediatrics* 2013; 131:128-40
Propranolol Consensus Guidelines

- Oral dosing (TID>>BID)
  - 1mg/kg/day up to 3mg/kg/day
  - Titrate based on response
- Duration of therapy
  - Variable but up to or beyond age 1 year
- Convenience of in-office initiation with monitoring
  - Exception age <8 weeks or high risk
- EKG only if concerns on exam / baseline HR
- Counseling on side effects

*Pediatrics* 2013; 131:128-40
Adverse Effects (all relatively rare)

- Major:
  - Bronchospasm
  - Hemodynamic
  - Hypoglycemia
  - Allergic reaction

- Minor:
  - Sleep disturbance
  - Acrocyanosis (cold hands/feet)
  - Somnolence
  - GI disturbance (diarrhea / reflux disease)
Propranolol

• Mechanism of action
  – Decreased VEGF production?
    » Smaller vessel diameter and blood flow
  – Inhibition of a hemangioma stem cell population
    » Promotes apoptosis and reduces proliferation

• Cessation of therapy can lead to rebound growth

Stem Cells Transl Med 2016; 5:45-55
Propranolol RCT

A Interim Analysis

B Week 24 Efficacy Analysis

Hemangeol®

- FDA approved in 2014
- Proprietary propranolol formulation
- Indicated for the treatment of proliferating infantile hemangio mas requiring systemic therapy
- Standardized dose escalation
- Approved for use up to 6 months’ duration

*N Eng J Med 2015; 372:735-46*
Topical Beta-blockers

- Timolol maleate 0.5% solution or gel-forming solution
  - Moderate to good effectiveness for thin superficial hemangiomas regardless of size
  - Adverse events minor (3.4% of 731 patients in retrospective review)
    - Local irritation (12)
    - Ulceration (4)
    - Brochospasm (3)
  - No cardiovascular side effects
- Option for those who want to avoid systemics

*Pediatrics* 2016; 138 [epub]
Future Options?

• Atenolol
  – Randomized Controlled Trial
    » As effective as propranolol in complete response
  – More selective
    » Spares β2 receptors
    » Reduced risk of sleep disturbance, bronchospasm, and hypoglycemic side effects

• Captopril
  – Randomized Controlled Trial
    » Inferior to propranolol in clinical response
    » Less effective at reducing VEGF levels

J Am Acad Dermatol 2014; 70:1045-9

When to Refer and Treat

- Earlier is Better!
- Parental Concern
- Location
  - Face (particularly around orifices), Neck, Lumbosacral, Groin, Hands/Feet
  - Periocular
    » Ophthalmology evaluation
  - Neck / Beard distribution
    » Recommend ENT evaluation – consider urgent if breathing / feeding issues
When to Refer and Treat

- **Number**
  - 3 or more is good rule
  - 5 or more is threshold for screening for visceral hemangiomas
- **Symptomatic**
  - Pain, Ulcerated, Crusting, Bleeding
- **Size**
  - 2.5cm or greater (especially off trunk)
- **Question of diagnosis**
- **Anytime / any age!**
Case 1
Case 1: Treatment

- Healthy 2 mo infant girl
- Solitary superficial hemangioma
  - Rapid growth
  - Parents concerned about cosmesis and impact on vision
- Opted for trial of topical therapy
  - Applied timolol 0.5% GFS 1-2 drops BID x 9 months
  - Tolerated well
Case 1: Outcome (4 months)
Case 1: Outcome (6 months)
Case 1: Outcome (12 months)
Case 2
Case 2: Treatment

- Healthy 4 mo infant girl
  - Parents not able to recall onset
  - Growing larger quickly
  - Painful when supine
  - Pediatrician concerned about diagnosis
- Biopsy confirmed infantile hemangioma
- Family elected for systemic therapy
  - Propranolol 20mg/5mL max dose 1.8mg/kg/day
  - Treated from 5 months of age to 17 months
  - Gaps in therapy – family held multiple times for URI
Case 2: Outcome (7 months)
Case 2: Outcome (2 years)
Case 3
Case 3: Treatment

- Presented as 5 mo infant girl
  - Rapid growth initially
  - Concerns about location
- Family initially concerned about systemic therapy
  - Treated with timolol 0.5% solution 2 drops BID from age 5 months to 9 months
- Elected for systemic therapy at 9 months
  - Oral propranolol 20mg/5mL max dose 2.6mg/kg/day from age 9 months until age 19 months
- Treatment of residual
  - Surgical excision vs observation and possible laser
Case 3: Outcome (10 months)
Case 3: Outcome (16 months)
Case 3: Outcome (19 months)
Case 4
Case 4: Treatment

- 2 mo infant female with “bruise” present at birth
  - Rapid growth and complicated by ulceration
- Treatment to prevent further ulceration as well as limit growth
  - Topical timolol 0.5% solution 3 drops BID for two months
  - Topical metronidazole gel to limit infection risk
  - Pulsed dye laser x 1 at age 4 months with response
  - Oral propranolol 20mg/5mL
    - Age 2 months – stopped after 2 weeks over concerns of sleep issues
    - Now ongoing – max dose 2.8mg/kg/day
Case 4: Outcome (4 months with ulceration)
Case 4: Outcome (6 months)
Case 5
Case 5: Treatment

- 4 mo adjusted age infant male
  - Born at 26 weeks GA, hemangiomas appeared while admitted
  - Upon discharge, sought treatment for ulceration, growth, bleeding, pain of leg hemangioma

- Treatment
  - Initial timolol 0.5% GFS topically BID x 2 weeks
  - Metronidazole gel topically BID
  - Wound care
  - Oral propranololol with good response
    » Max dose 1.6mg/kg/day - ongoing
Case 5: Outcome (10 months adjusted age)
When to Refer and Treat

- Earlier is Better!
- Parental Concern
- Location
  - Face (particularly around orifices), Neck, Lumbosacral, Groin, Hands/Feet
  - Periocular
    » Ophthalmology evaluation
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- **Size**
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- **Question of diagnosis**

- **Anytime / any age!**
Thank You!

- Please do not hesitate to contact me with questions
  - jjoyce@northshore.org
  - 847-663-8060