AAP Infantile Hemangioma Webinar

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Disclaimer

- Dr. Frieden discloses that she is chair of data safety monitoring boards for Pfizer (studies not related to hemangiomas), consultant for Venthera/Biobridge (developing therapy for vascular malformations), co-president of Pediatric Dermatology Research Alliance, and president of International Society for the Study of Vascular Anomalies.

- Dr. Mancini discloses that he participated in a scientific advisory board in 2018 with Pierre Fabre, for which he received an honorarium.

- Statements and opinions expressed are those of the authors and not necessarily those of the American Academy of Pediatrics (AAP).

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Background

- Infantile hemangiomas (IHs) are one of the most common birthmarks of childhood.
  - Present in ~4% of newborns and up to 15% of preterm infants
- IHs are benign growths and they involute spontaneously.
- Pediatricians are often taught a “hands-off” approach:
  - Why treat something benign that will go away on its own?
- For most IHs seen by pediatricians, this is correct; BUT there are many exceptions.
- For those requiring intervention, there’s a time-sensitive window to act and prevent complications.
Development of the AAP Clinical Practice Guideline (CPG) on IHs

- The AAP has never had a CPG on this topic.
- In 2015 the AAP recommended that the US Agency for Healthcare Research and Quality (AHRQ) study IHs systematically.
  - Recognition that “things had changed”
  - AHRQ report issued in 2016
- The AAP convened a multidisciplinary group in December 2016 to write the CPG.
- The CPG used this AHRQ and updates through January 2017 as the basis for a multi-disciplinary consensus-guided document.

Clinical Practice Guideline for the Management of Infantile Hemangiomas

IHs – Common Myths

1. They all go away.
2. Because of #1, treatment is usually unnecessary.
3. The skin will be normal once the IH is gone.
4. Most IHs are gone by 1–2 years of age.
5. Complications related to IHs are rare so I don’t need to worry.
Parents often figure it out...

- But it may be too late
- Sources of information:
  - Friends/family
  - Websites
  - Mommy/daddy groups
  - Social media (ie, Facebook IH parent groups)
Referred at one year
Referral at 5 months
Post-involution Sequelae

Important to consider

Should be part of medical decision-making when deciding “to treat or not to treat”
Same patient

2 mos

3 years

7 years
Key Take-Aways From the CPG

- Most IHs are small and innocuous but a significant minority are problematic
- Gives a risk stratification schema
- Emphasizes critical need for early referral for high-risk IH “window of opportunity”
- Defines: What is a “hemangioma specialist?”
Small spot on cheek of 4-week-old

What should pediatrician do?

1. Reassure this is benign and will go away.
2. Recheck again at next well-baby check-up.
3. Urgent referral to dermatologist.
4. Start topical timolol.
5. Start oral propranolol.
If we look back...

Weeks of life

2 4 6 8 10
Small spot on left abdomen in this newborn

What is the best next step?

1. Reassure this is benign and will go away.
2. Recheck again at next well-baby check-up.
3. Urgent referral to dermatologist.
4. Start topical timolol.
5. Start oral propranolol.
IH — Risk Stratification
CPG Defines 4 Risk Categories: Highest, High, Intermediate, and Low

- Highest and high categories typically require consultation, either in person or via telemedicine or teletriage.

- THESE INCLUDE:
  - Potential for life-threatening complications
  - Risk underlying abnormalities
  - Functional impairment
  - **Potential causing permanent disfigurement**
  - Ulceration
Risk Stratification and Need for Consultation

- Highest risk: Timing ≤1 week
- High risk: Timing ≤2 weeks
- Intermediate risk: May or may not need consultation/referral
- Low risk: Typically will not need consultation/referral

High

- Large segmental IH on trunk or extremities:
  - Risk of scarring and/or disfigurement.
- Any facial IH ≥2 cm (>1 cm if ≤3 mo of age):
  - High risk of scarring and/or disfigurement.
- Nasal tip or lip IH even if <1 cm:
  - High risk of scarring and/or permanent distortion of anatomic landmarks.
- Oral:
  - Risk of ulceration or bleeding, may interfere with feeding.
- Neck or scalp IH >2 cm during growth phase:
  - Risk of ulceration (neck)
  - Risk of ulceration, scarring, and/or hair loss (scalp).
- Breast:
  - Risk of permanent changes in breast development (eg, breast asymmetry)
    or nipple contour.
- Ulcerated hemangioma (any site):
  - Risk of severe pain, scarring and/or disfigurement, and bleeding.

Segmental IH on extremities: higher risk of ulceration; permanent skin changes, such as thickening, atrophy, or scarring

≥5 or more cutaneous hemangiomas (at any anatomic site) may be associated with hepatic hemangiomas

Perineal or perianal IH: increased risk of ulceration

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American Academy of Pediatrics

MeadJohnson Nutrition

IJF
Small lesions on torso are lower risk:
- Less likely to be disfiguring
- Typically do not require active intervention

Segmental lumbosacral or perineal IH:
- Higher risk of ulceration
- May be associated with underlying structural anomalies (eg, LUMBAR syndrome)

Risk of LUMBAR syndrome
Why we picked 1 cm in young infants?
<table>
<thead>
<tr>
<th>Intermediate</th>
<th>Low</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Perineal IH (localized) without ulceration:</td>
<td></td>
</tr>
<tr>
<td>○ potential for ulceration in this location.</td>
<td></td>
</tr>
<tr>
<td>• Trunk or extremity IH &gt;2 cm especially in growth phase or if abrupt transition from normal to affected skin (ie, ledge effect; Fig 8):</td>
<td></td>
</tr>
<tr>
<td>○ risk of scarring and/or disfigurement.</td>
<td></td>
</tr>
<tr>
<td>• IH &lt;2 cm on trunk or extremities in areas easily covered by clothing.</td>
<td></td>
</tr>
<tr>
<td>• IH on trunk or extremities &gt;2 cm if gradual transition from normal to affected skin (Fig 13).</td>
<td></td>
</tr>
</tbody>
</table>

Age 6 Months – 3 IHs
Each one a little different, all low risk
The Critical Role of Timing
Evolution of Hemangioma Growth Over 3 Months

Growth Characteristics of Early IH

Most rapid rate of growth is between 5.5–7.5 weeks.
Treatment initiation should occur early.

IH – Growth Phases

2 dynamic phases:

**Proliferative** – early infancy
Most rapid growth between 1–2 months; 80% of IH size reached by 3 months; most growth complete by 5 months
Deep IH may appear later and grow longer

**Involution** – starts by one year
Majority of involution occurs by age 4 years
50%–70% resolve
May leave behind telangiectasia, fibrofatty tissue, anetoderma, scar

Referred at 10 months
Referred at 6 months
Referred at 4 months
Defining “Hemangioma Specialist”

- Management of IHs is not limited to 1 medical or surgical specialty.
- A hemangioma specialist may have expertise in dermatology, hematology-oncology, pediatrics, facial plastic and reconstructive surgery, ophthalmology, otolaryngology, pediatric surgery, and/or plastic surgery, and his or her practice is often focused primarily or exclusively on the pediatric age group.
More on “Hemangioma Specialist”

- Understand the time-sensitive nature of IHs during the growth phase and be able to accommodate requests for urgent evaluation
- Have experience with accurate risk stratification and potential complications associated with IHs
  - Able to provide recommendations for various management options and to discuss R/B/A for specific patients
  - Knowledge of past and emerging medical literature regarding IHs
Resources for Parents and Physicians

- Many charts, graphs, supplementary materials
- Goal: Trying to make it easier for PCPs to gain confidence in IH management and referral
- Handouts for parents
  - General IH information
  - Information re: propranolol
  - Medication handout
Management Algorithm of IH in Infants ≤3 Months of Age

Figure 2
High-risk IHs involving the face and neck.

Figure 3
High-risk IHs involving the trunk, extremities, and perineum.

Figure 4
IHs involving the posterior trunk.

**SUPPLEMENTAL TABLE 22 Risk Level of IHs of Varying Types**

Using this table, assess the risk posed by the infantile hemangioma you are evaluating. On the reverse side of the page use the flow diagram to determine the action recommended based on risk.\(^a\,^{b}\)

<table>
<thead>
<tr>
<th>Risk Level</th>
<th>Clinical Examples and Reason(s) for Concern</th>
</tr>
</thead>
</table>
| **Highest** | • Large (>5 cm) or segmental facial or scalp:  
  ○ higher risk of airway hemangiomas (if beard area),  
  ○ may be associated with PHACE syndrome,  
  ○ high risk of scarring and/or disfigurement.  
  • Large or segmental lumbosacral or perineal:  
  ○ may be associated with LUMBAR syndrome  
  ○ high risk of ulceration and scarring.  
  • Multifocal IHs (≥5) and abdominal ultrasonography reveals liver hemangiomas:  
  ○ may be associated with abdominal compartment syndrome, high-output congestive heart failure, and hypothyroidism.  
  • Periocular IH causing eyelid asymmetry, lid closure or ptosis, proptosis, or other findings with potential impact on visual axis:  
  ○ risk of astigmatism, anisometropia, and amblyopia.  
  • Large segmental IH on trunk or extremities:  
  ○ risk of scarring and/or disfigurement.  
  • Any facial IH ≥2 cm (>1 cm if ≤3 mo of age):  
  ○ high risk of scarring and/or disfigurement.  
  • Nasal tip or lip IH even if <1 cm:  
  ○ high risk of scarring and/or permanent distortion of anatomic landmarks.  
  • Oral:  
  ○ risk of ulceration or bleeding, may interfere with feeding.  
  • Neck or scalp IH ≥2 cm during growth phase:  
  ○ risk of ulceration (neck)  
  ○ risk of ulceration, scarring, and/or hair loss (scalp).  
  • Breast:  
  ○ risk of permanent changes in breast development (eg, breast asymmetry) or nipple contour.  
  • Ulcerated hemangioma (any site):  
  ○ risk of severe pain, scarring and/or disfigurement, and bleeding.  |
| **High** | • Localized IH (localized) without ulceration:  
  ○ potential for ulceration in this location.  
  • Trunk or extremity IH >2 cm especially in growth phase or if abrupt transition from normal to affected skin (ie, ledge effect; Fig 8):  
  ○ risk of scarring and/or disfigurement.  |
| **Intermediate** | • IH <2 cm on trunk or extremities in areas easily covered by clothing.  
  • IH on trunk or extremities >2 cm if gradual transition from normal to affected skin (Fig 13). |

\(^a\) See photographic examples at https://downloads.aap.org/CCSA/CPG_IH_Example_Photos.pdf

\(^b\) Consultation with a hemangioma specialist may involve a telephone conversation and/or electronic transmission of patient photographs.

CPG Supplementary Information

- Patient information
  - General IH information
  - Information re: propranolol
  - Medication handout
- Table defining highest, high, intermediate, low risk IH
- Management algorithm

pediatrics.aappublications.org/content/pediatrics/suppl/2018/12/19/peds.2018-3475.DCSupplemental/PEDS_20183475SupplementaryData.pdf
IH – Management
Oral Propranolol
### TABLE 11 Key Action Statement 3A: Clinicians should use oral propranolol as the first-line agent for IHs requiring systemic treatment (grade A, strong recommendation).

<table>
<thead>
<tr>
<th>Aggregate Evidence Quality</th>
<th>Grade A</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benefits</td>
<td>Improve IH treatment; avoid adverse effects associated with oral steroid therapy</td>
</tr>
<tr>
<td>Risks, harm, cost</td>
<td>Occurrence of adverse effects associated with propranolol use (see KAS 3D); medication cost and cost of hospitalization if drug is initiated while infant is an inpatient</td>
</tr>
<tr>
<td>Benefit-harm assessment</td>
<td>Benefits outweigh harms</td>
</tr>
<tr>
<td>Intentional vagueness</td>
<td>None</td>
</tr>
<tr>
<td>Role of patient preference</td>
<td>Parents should be involved in shared decision-making regarding treatment</td>
</tr>
<tr>
<td>Exclusions</td>
<td>Caution (but not exclusion) in infants &lt;5 wk of age, postconceptual age of &lt;48 wk; potential exclusions that require appropriate subspecialty evaluation and/or clearance; evidence of cardiogenic shock or heart failure; sinus bradycardia; heart block greater than first degree; known or suspected PHACE syndrome, including presence or risk of coarctation of the aorta and cerebrovascular anomalies; known asthma and/or reactive airway disease; known hypersensitivity to propranolol</td>
</tr>
<tr>
<td>Strength</td>
<td>Strong recommendation</td>
</tr>
<tr>
<td>Key references</td>
<td>3,46,59–61</td>
</tr>
</tbody>
</table>

History – Propranolol in Kids

- Long history of off-label use in children
  - Dysrhythmias, especially SVT
  - Tetralogy of Fallot
  - Congestive heart failure
  - Hypertension
  - Hypertrophic cardiomyopathy
  - Thyrotoxicosis
  - Migraines

Evolution: β-blockers & IH

- 2009: Literature expands (derm, ophtho, ENT); English, German, French, Spanish
- 2010: First-line systemic therapy for most peds derms
- 2010–2012: Prospective, multicenter, international collaborative study (“Hemangiol”; Pierre Fabre Dermatologie, Boulogne, France)
- 2014: Hemangeol approved (FDA – March; EMA – April)

### TABLE 13 Key Action Statement 3B: Clinicians should dose propranolol between 2 and 3 mg/kg per day unless there are comorbidities (eg, PHACE syndrome) or adverse effects (eg, sleep disturbance) that necessitate a lower dose (grade A, moderate recommendation).

<table>
<thead>
<tr>
<th>Aggregate Evidence Quality</th>
<th>Grade A</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benefits</td>
<td>The recommended doses have been associated with high clearance rates of IH</td>
</tr>
<tr>
<td>Risks, harm, cost</td>
<td>Response rates for higher or lower doses have not been well studied</td>
</tr>
<tr>
<td>Benefit-harm assessment</td>
<td>Benefits outweigh harms</td>
</tr>
<tr>
<td>Intentional vagueness</td>
<td>None</td>
</tr>
<tr>
<td>Role of patient preference</td>
<td>Parents will be involved in the decision about dosing in the setting of PHACE syndrome or the occurrence of adverse effects</td>
</tr>
<tr>
<td>Exclusions</td>
<td>See KAS 3A: dosing may be modified if comorbidities exist</td>
</tr>
<tr>
<td>Strength</td>
<td>Moderate recommendation</td>
</tr>
<tr>
<td>Key references</td>
<td>1,46,61,76</td>
</tr>
</tbody>
</table>

### TABLE 14 Key Action Statement 3C: Clinicians should counsel that propranolol be administered with or after feeding and that doses be held at times of diminished oral intake or vomiting to reduce the risk of hypoglycemia (grade X, strong recommendation).

<table>
<thead>
<tr>
<th>Aggregate Evidence Quality</th>
<th>Grade X</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benefits</td>
<td>Reduce the likelihood of adverse reactions</td>
</tr>
<tr>
<td>Risks, harm, cost</td>
<td>Risk that parents will decline therapy because of concerns about potential medication adverse effects</td>
</tr>
<tr>
<td>Benefit-harm assessment</td>
<td>Benefits outweigh harms</td>
</tr>
<tr>
<td>Intentional vagueness</td>
<td>None</td>
</tr>
<tr>
<td>Role of patient preference</td>
<td>None</td>
</tr>
<tr>
<td>Exclusions</td>
<td>None</td>
</tr>
<tr>
<td>Strength</td>
<td>Strong recommendation</td>
</tr>
<tr>
<td>Key references</td>
<td>46,60,61,76,78–80</td>
</tr>
</tbody>
</table>
TABLE 15  Key Action Statement 3D: Clinicians should evaluate patients for and educate caregivers about potential adverse effects of propranolol, including sleep disturbances, bronchial irritation, and clinically symptomatic bradycardia and hypotension (grade X, strong recommendation).

<table>
<thead>
<tr>
<th>Aggregate Evidence Quality</th>
<th>Grade X</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benefits</td>
<td>Recognition of adverse effects of propranolol treatment</td>
</tr>
<tr>
<td>Risks, harm, cost</td>
<td>Risk of caregivers declining medical therapy because of concern about potential adverse effects</td>
</tr>
<tr>
<td>Benefit-harm assessment</td>
<td>Benefits outweigh harms</td>
</tr>
<tr>
<td>Intentional vagueness</td>
<td>None</td>
</tr>
<tr>
<td>Role of patient preference</td>
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<tr>
<td>Exclusions</td>
<td>None</td>
</tr>
<tr>
<td>Strength</td>
<td>Strong recommendation</td>
</tr>
<tr>
<td>Key references</td>
<td>3, 46, 61, 76, 80, 85–88</td>
</tr>
</tbody>
</table>

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Outcomes Variable but Better than Without Rx

6 wks

1 yr

7 yrs
Even Starting Late Propranolol Can Improve Outcomes (Sometimes)
Topical Timolol – 2019

- First use reported in 2010
- Now >100 PubMed citations, numerous case series, reports, and a few clinical trials
- **Best response** in superficial IHs <1 mm thick
  - In selected patients ~7%–10% require subsequent therapy with oral β-blocker
- Adverse events are uncommon (~3%) and mild

Timolol – Should Pediatricians Be Using It?

- Off-label use; some does get absorbed
- More potent than propranolol at beta blockade
- Most absorption in thick hemangiomas (where it doesn’t work well anyway)

IF YOU USE

- Limit to 1 drop BID-TID
- Caution in preterm infants
- If <3 months need to watch very closely for growth that may require systemic medication

2 months

3 mos Rx timolol
Shared Decision-Making

- Even for low and intermediate IHs some parents will want to consider Rx.
- Rapid growth can be a time of high anxiety.
- Google images can be very frightening.
- Important concepts:
  - Hemangiomas “mark out their territory early”
  - Growth thereafter is volumetric
  - Bleeding is often feared but excessive bleeding is very uncommon
  - Steer parents to vetted sources (e.g., Healthy Children website and others listed in CPG)
Infantile Hemangiomas: 2019

- Highly effective IH therapy is available.
- AAP CPG tells PCPs who to refer and gives guidance re: timing of referral.
- Goal of CPG group is to “move the needle” on more prompt and appropriate referrals.
- Implementation challenges remain.
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