Supplemental Information

**IH TYPES: CLASSIFICATION OF IHs**

IHs are classified on the basis of their soft-tissue depth (superficial, combined, and deep) and pattern of anatomic involvement (localized, segmental, and multifocal). Some examples are presented in Supplemental Figs 5–10.

**SUPPLEMENTAL FIGURE 5**
Localized superficial IH. Bright red with little or no subcutaneous component (formerly called a strawberry hemangioma or mark). Small lesions, such as this, typically require no intervention. However, if the lesion was located on the face, the management approach might differ (courtesy of A.J.M.).

**SUPPLEMENTAL FIGURE 6**
Localized combined (or mixed) IH. There is a bright red superficial component and a deep component with a bluish color (courtesy of D.P.K.).

**SUPPLEMENTAL FIGURE 7**

**SUPPLEMENTAL FIGURE 8**
IH that covers a territory/large anatomic region; these often measure greater than 5 cm. When on the face, such as this IH, there is a very high risk, both for scarring and associated extracutaneous disease (eg, PHACE syndrome and, if in “beard area,” airway IH) (courtesy of D.P.K.).

**SUPPLEMENTAL FIGURE 9**
Segmental IH variant: IH with minimal or arrested growth (IH-MAG). As the name suggests, these lesions undergo minimal or no proliferation. (Localized IH can also have features of IH-MAG.) In this IH-MAG, the bright red spots represent areas of minimal proliferation. IH-MAGs may resemble port-wine stains but often have visible telangiectasias, as shown here (courtesy of D.P.K.).

**SUPPLEMENTAL FIGURE 10**
Multifocal IH. This infant has multiple discrete lesions. She also had multiple hepatic hemangiomas and high-output congestive heart failure (courtesy of D.P.K.).
METHODS

On November 14, 2013, the AAP, on behalf of stakeholder organizations,* nominated the topic of the diagnosis and management of IHs to the Effective Health Care Program (EHCP) of the AHRQ with the intent of using the information gathered to develop a CPG. The EHCP provides evidence about the comparative effectiveness of different medical interventions. The goal is to assist consumers, health care providers, and others make informed choices among various management options. By conducting comparative effectiveness reviews, the EHCP supports systematic assessments of scientific evidence regarding treatments for important disorders. The topic nominated by the AAP was accepted by the EHCP.

The AHRQ conducted a comprehensive review of potential benefits of diagnostic modalities and pharmacologic and surgical treatments as well as possible associated harms. Their methodology and the report, including the evidence search and review that the AHRQ conducted, are available in their entirety and as an executive summary on the AHRQ Web site.4

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Key Questions

The key questions (KQs) and contextual questions that were developed by the AHRQ in consultation with key informants and were posted on the Effective Health Care Web site are presented in Supplemental Table 21.

Study Selection

Admissible study designs for the AHRQ review for contextual questions (which included policy at local, state, and national levels; community means and resources; physician incentive systems; practice history and staffing; and cultural issues) were as follows:

- systematic reviews;
- articles reporting on the history of IH diagnosis or treatment;
- practice guidelines, meta-analyses, RCTs, and case series with at least 25 children with IHs; and
- any comparative studies.

Admissible designs for comparative effectiveness key questions for both the AHRQ and the CPG subcommittee updated review were as follows:

- imaging accuracy: RCTs and any comparative studies;
- benefits of interventions: RCTs and any comparative studies; and
- harms of interventions: RCTs, any comparative studies, and case series with at least 25 children with IHs.

Study Review

For the AHRQ analysis, 2 reviewers independently assessed each abstract. If 1 reviewer concluded that the article was eligible to address a key question on the basis of the abstract, it was retained for a full-text review. The AHRQ did not conduct

SUPPLEMENTAL TABLE 21 Key Questions and Contextual Questions Developed by the AHRQ

<table>
<thead>
<tr>
<th>Question</th>
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<tbody>
<tr>
<td>KQ1</td>
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<tr>
<td>KQ2</td>
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<tr>
<td>KQ3</td>
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<td>KQ4</td>
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<tr>
<td>CQ1</td>
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<tr>
<td>CQ2</td>
</tr>
</tbody>
</table>

The subcommittee also included general surgery, plastic surgery, and radiology. Dermatology, cardiology, hematology—composed of IH experts in the fields of a multidisciplinary subcommittee.

In December 2016, the AAP convened Practice Guideline Development of the Clinical Practice Guideline. Decisions and the strength of recommendations were based on a systematic grading of the quality of evidence by independent reviewers. Expert consensus was used when definitive data were not available. KASs (summarized in Table 4) were generated by subcommittee members authoring individual components of the CPG using the results of the literature review. These sections were reviewed and refined by the subcommittee chair and cochair and ultimately by all subcommittee members.

Evidence-based guideline recommendations from the AAP may be graded as strong, moderate, weak on the basis of low-quality evidence, or weak on the basis of balance between benefits and harms. Strong and moderate recommendations usually are associated with “should” and “should not” recommendation statements, whereas some moderate and all weak recommendation may be recognized by the use of “may” or “need not,” signifying that moderate recommendations are based on a range of evidence strengths within the boundaries of the definition (Fig 1, Table 5).

- A strong recommendation means that the committee’s review of the evidence indicates that the benefits of the recommended approach clearly exceed the harms (or, in the case of a strong negative recommendation, that

This guideline is intended for use primarily by clinicians providing care for infants who have IHs and their families. This guideline may be of interest to parents and payers, but it is not intended to be used for reimbursement or to determine insurance coverage. This
guideline is not intended as the sole source of guidance in the evaluation and management of IHs, but rather, it is intended to assist clinicians by providing a framework for clinical decision-making.

SUPPLEMENTAL REFERENCES

FROM THE AMERICAN ACADEMY OF PEDIATRICS

INFORMATION FOR FAMILIES: WHAT ARE HEMANGIOMAS?

Hemangiomas are groups of extra blood vessels in the skin. They are not cancerous and usually appear during the first weeks of life.

Superficial hemangiomas are bright red and bumpy. They are often called strawberry marks because they look like the surface of a strawberry. Deep hemangiomas occur under the skin and have a bluish color. Some hemangiomas have superficial and deep parts. Hemangiomas that are present at birth are different; these are called congenital hemangiomas.

What to Expect

Hemangiomas usually grow in the first 2 to 3 months of life. Most growth is complete by 6 months of age. Deep hemangiomas can sometimes grow for a longer time. At between 6 and 18 months of age, most hemangiomas begin to improve. The hemangioma will be less red and will take on a gray color. It will also get softer and flatter. Improvement in the hemangioma often takes many years. Most improvement happens by age 4 years, but sometimes, it takes longer.

Possible Complications

Most hemangiomas cause no problems and can be left to go away on their own. Parents often worry about hemangiomas bleeding. This is rare and only happens if the skin has broken down (ulcerated). The bleeding usually lasts a short time and stops with gentle pressure.

Hemangiomas usually do not cause pain unless the skin has broken down.

Hemangiomas can cause permanent changes in the skin’s texture or color or leave lumpiness even after the hemangioma has gone away. This can be worrisome, especially for hemangiomas on the face. In rare cases, hemangioma may affect eating, eyesight, hearing, or breathing.

Does a Hemangioma Need to Be Treated?

Whether a hemangioma needs treatment depends on the age of the patient, where the hemangioma is located, how fast it is growing, and whether it might cause problems. There are 3 main reasons for treatment:

1. a medical problem caused by the hemangioma;
2. a breakdown of the hemangioma skin that may cause skin damage or scarring; and
3. concern about permanent skin changes.

Possible Treatments

Local Treatments

β-blocker, a medication, like timolol solution, is applied to the hemangioma. This can help stop the hemangioma from growing. Sometimes it can shrink and fade a hemangioma, especially if the hemangioma is not thick.

With steroid injection, a steroid can be injected into the hemangioma. This works best for hemangiomas that are localized and are becoming thick.

Oral Treatments

Propranolol is a medicine taken by mouth that is used to treat hemangiomas. It has been used for many years to treat high blood pressure. Oral steroids sometimes are used, but propranolol is more effective.

Other Treatments

Lasers may be helpful to remove some of the redness after hemangiomas have begun to go away or have finished their improvement phase.

Surgery sometimes is performed if oral treatments fail. Surgery also can be performed to repair leftover extra skin or scarring. Because surgery leaves a scar (and because most hemangiomas get better with time), early surgery usually is not needed. Surgery is sometimes performed if the skin of the hemangioma breaks down.

For more information, visit www.hemangiomaeducation.org (sponsored by the Hemangioma Investigator Group).

Adapted with permission from “What Are Infantile Hemangiomas?” published by the Society for Pediatric Dermatology (contributing Society for Pediatric Dermatology members: Brandi Kenner-Bell, Amjad Khan, and Liborka Kos; committee reviewers: Andrew Krakowski and Aimee Smidt; expert reviewer: Ilona Frieden).

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INFORMATION FOR FAMILIES: PROPRANOLOL FOR HEMANGIOMAS

Hemangiomas are groups of extra blood vessels in the skin. They usually appear during the first weeks of life. Hemangiomas may grow in the first 2 to 3 months of life. At between 6 and 18 months of age, most hemangiomas begin to improve.

When Do Hemangiomas Need to Be Treated?
Most hemangiomas cause no problem and may be left to improve on their own. Whether a hemangioma needs treatment depends on the age of the patient, where the hemangioma is located, how fast it is growing, and whether it might cause problems. There are 3 main reasons for treatment:

- a medical problem caused by the hemangioma;
- a breakdown of the hemangioma skin that may cause skin damage or scarring; and
- concern about permanent skin changes.

What Is Propranolol and How Does It Work?
Propranolol is a β-blocker. It has been used for many years to treat problems such as high blood pressure and irregular heartbeat. Propranolol also may make hemangiomas better. It makes them softer and less red. It also can make them smaller. Propranolol works quickly. Improvement may be seen in the first few days to weeks on the medication.

Are Any Tests Needed Before Starting Propranolol?
Most infants require no testing. Occasionally, your doctor may order an electrocardiogram. You should speak with your doctor about what testing may be needed for your child.

What Are the Possible Side Effects of Propranolol?
Propranolol can have side effects, but they are uncommon. Possible side effects include:

- Slow heart rate and low blood pressure are rare side effects. Most infants taking propranolol have a normal heart rate and blood pressure. Some have changes so mild that they cause no problem.
- Low blood sugar is a rare side effect, but it may be a serious one. Low blood sugar can cause infants to be weak, fussy, shaky, or nervous. Rarely, it can cause a seizure. Low blood sugar usually happens if an infant is not feeding well or has gone a long time without feeding. To help prevent this, propranolol should always be given just before or just after a feeding. If your infant is not feeding well, propranolol should be stopped until feeding returns to normal.
- Breathing trouble (wheezing or cough) usually happens when an infant has a cold. To be safe, it is best to stop propranolol until the cold improves.
- Changes in sleep: some infants have trouble falling asleep, sleep more than normal, or have nightmares. This usually happens during the first weeks of treatment and often improves with time.
- Other possible side effects: some infants develop cool hands and feet. Stomach problems like diarrhea or constipation rarely occur.

Notify your provider if you have questions about propranolol or concerns about your infant’s health.

How Is Propranolol Taken?
Propranolol is taken by mouth, and the dose will be calculated on the basis of your child’s weight. It is given 2 or 3 times per day 6 to 8 hours apart. Propranolol should always be given just before or after a feeding.

How Long Does Treatment With Propranolol Last?
The length of treatment will depend on your child’s individual situation. Most infants are treated until about 12 to 15 months of age.

Adapted with permission from “Propranolol for Infantile Hemangiomas” published by the Society for Pediatric Dermatology (contributing Society for Pediatric Dermatology members: Brandi Kenner-Bell, MD, and Liborka Kos, MD; committee reviewers: Brandi Kenner-Bell, MD, and Andrew Krakowski, MD; expert reviewer: Anthony J. Mancini, MD).

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MEDICATION INFORMATION

Propranolol Treatment of IHs

Child’s name: ____________________

______________________________

____

Date: ____________________

Your infant’s weight today is ___________________

Giving the Medicine

Usually, propranolol is given 2 times a day. Sometimes it is given 3 times a day. If this is the case, your provider will give you separate instructions.

Give ________ mL 2 times a day.

Additional instructions: ______________

________________________________

________________________________

________________________________

________________________________

________________________________

Give a dose in the morning and a dose in the afternoon (at least 6 hours after the morning dose).

Each dose should be given immediately before, during, or after a feeding.

If your infant is sick or not taking his or her usual amount of milk and/or formula, do not give propranolol until feeding returns to normal. This prevents the blood sugar from dropping.

What Side Effects May Occur?

Side effects are uncommon. Some that may occur are listed here. If you have questions about side effects, please call us.

• Low pulse and blood pressure happen rarely and usually are mild.

• Low blood sugar is a rare side effect. Infants may seem weak, irritable, shaky, or nervous.

• Breathing trouble (wheezing or cough) usually occurs at the time an infant has a cold. To be safe, it is best to stop propranolol until your infant is seen by your provider or the cold improves.

• Changes in sleep may include trouble falling asleep or staying asleep, sleeping more than usual, or nightmares. Changes in sleep usually happen during the first weeks of treatment and may get better over time.

• Cool hands and feet may occur.

• Stomach problems like diarrhea or constipation may occur.

Call 9-1-1 immediately if your child is difficult to wake up, floppy, or having trouble breathing.

Our telephone number is ___________________________
### 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.**

<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. |
| **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. |
| **Intermediate** | • Perineal 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. |
| **Low** | • 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/DOCCSA/CPC_IH_Example_Photos.pdf.

*b* Consultation with a hemangioma specialist may involve a telephone conversation and/or electronic transmission of patient photographs.
Action needed for an infant \( \leq 3 \) months of age being seen with an IH. Repeat evaluations may be performed during an office visit or by transmitting photographs of the lesion via e-mail or the electronic medical record. If photographs are used, parents may be advised to send 1 photograph taken from 12 to 18 in (for perspective and anatomic context) and a closer view. Parents should also be advised to measure the diameter of the lesion.