Comparative Effectiveness Review
Number 168

Effective Health Care Program

Diagnosis and Management of Infantile Hemangioma

Executive Summary

Introduction

Infantile hemangiomas (IH) are the most common tumors of childhood. IH are benign but possess potential for local tissue damage, ulceration, infection, bleeding, functional impact, and pain. The International Society for the Study of Vascular Anomalies classifies IH as vascular tumors that are differentiated from vascular malformations in several ways including natural history, cellular composition, immunohistochemical expression, and pathology.[1] Due to historical inconsistencies in naming conventions, it is difficult to understand the true prevalence of IH, but it is estimated that they affect about 4 to 5 percent of children,[2] with higher prevalence in females and Caucasians.[3,4] IH tend to go through growth and involution phases, although the complete natural history of IH by various characteristics has not been described. In most children, IH will become apparent in the first few weeks of life and reach 80 percent of total size by around age 3 to 5 months.[5,6] With a course of expectant observation, many patients may experience a complete involution without significant sequelae; however, IH frequently occur in cosmetically and functionally sensitive areas. Even with complete involution, some patients have permanent disfigurement and functional compromise.[7] Early assessment of the extent of the hemangioma, and early, appropriate treatment of IH may potentially mitigate these complications; however, in

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The Effective Health Care Program was initiated in 2005 to provide valid evidence about the comparative effectiveness of different medical interventions. The object is to help consumers, health care providers, and others in making informed choices among treatment alternatives. Through its Comparative Effectiveness Reviews, the program supports systematic appraisals of existing scientific evidence regarding treatments for high-priority health conditions. It also promotes and generates new scientific evidence by identifying gaps in existing scientific evidence and supporting new research. The program puts special emphasis on translating findings into a variety of useful formats for different stakeholders, including consumers.

The full report and this summary are available at **www.effectivehealthcare.ahrq.gov/reports/final.cfm**.

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one large multicenter treatment analysis, the first specialist visit for children in the study did not occur until a mean of 5 months of age.[6]

Furthermore, some lesions are particularly aggressive or morbid and can cause severe pain, ulceration, and bleeding even in early stages.[8,9] The rapid growth of IH leaves little time for prospective observation to determine which IH will lead to complications and require specialist attention and treatment before complications begin to manifest. Some types of IH, specifically segmental hemangiomas, are recognized as high risk, but no consensus exists on which non-segmental lesions warrant referral for appropriate treatment to mitigate future complications (e.g., bleeding, ulceration) of the hemangioma or long-term sequelae (e.g., scarring, anatomical disfigurement, functional complications).[10-12]

Diagnosis and Treatment Decisions

Evaluation through the use of various diagnostic imaging modalities has been generally reserved for deep lesions to help understand their extent or to confirm the diagnosis of IH. Purely cutaneous lesions do not require imaging, but opinions regarding the initial diagnostic test of choice for more extensive IH, including deep, segmental, and syndromic lesions, are conflicting. Furthermore, different disease sites or extents may be best handled with different imaging modalities. The questions of imaging necessity and type are especially important because imaging studies in infants often require general anesthesia and may be associated with adverse effects. Modalities such as computed tomography also involve exposure to radiation.

Specific disease characteristics, such as lesion size, location, rate of growth, and persistence as well as modifiers such as patient age, functional impact, and IH subtype influence whether children are treated with pharmacologic agents or surgically. Many lesions can be treated with pharmacologic agents; however, refractory lesions that possess immediate risk for morbidity or mortality, such as hemangiomas obstructing the airway or visual axis, may require more immediate surgical intervention. Lesion characteristics such as size, location, and type (e.g., superficial, deep) also influence the choice of specific pharmacologic agents. For example, small, superficial lesions may respond well to topical agents such as timolol, while deep lesions are less likely to respond.[13] Intralesional steroids may be the drug of choice for bulky, localized IH but are likely to be less effective for extensive superficial IH. Both medical and surgical treatment paradigms contain significant variability and lack of consensus.

In many cases of IH, early referral and intervention are crucial to a satisfactory outcome and to mitigate structural changes to adjacent structures or disfiguring sequelae. In addition to structural damage, the psychological complications of having facial differences must be considered when determining the need for referral or treatment. While well-recognized clinical signs such as ulceration, airway obstruction, or vision-threatening involvement indicate need for urgent referral, there are no discrete guidelines that help direct primary care providers on when to refer patients with IH for subspecialty care.

Interventions

The beta-blocker propranolol was approved by the U.S. Food and Drug Administration (FDA) for use in IH in March 2014[14-16] and was historically used in children for cardiac conditions and off-label to treat IH after the serendipitous discovery of its effects on IH lesions in 2008.[17] Prior to this, corticosteroids were the drug of choice, but propranolol has become the typical choice for initial medical management in children without contraindications to beta-blockers. Steroids may be used in children with contraindications to beta-blockers or who do not respond to beta-blockers. Additionally, there is no clear consensus as to when alternative or adjunctive or historically used medications such as chemotherapeutic drugs are appropriate if first-line treatment is unsuccessful.[18,19]

Surgical interventions for IH can be used for primary management of high risk lesions by resection or ablation using laser or radiofrequency. Some confusion and disagreement exists about what type of surgical treatment to use, when in the disease course to treat, and how the disease site informs treatment decisions. Interventions for IH are varied, involved, and not without risk (e.g., risk of permanent hypopigmentation, scarring from pulsed dye laser therapy, potential harms of anesthesia); therefore, universal treatment is unwarranted.

Scope and Key Questions

Scope and Uses of the Review

This systematic review addresses the evidence for benefits and harms of commonly used treatments for children (ages 0-18 years) with IH: beta-blockers, corticosteroids, "second-line" drugs used after the failure of beta-blockers or steroids, and laser and surgical treatment. The decisional dilemmas that this review addresses are whether imaging modalities are useful both in diagnosis and for guiding treatment, and the expected comparative

effectiveness (benefits and harms) of pharmacologic and surgical treatments, relative to observation or other active treatments. While pharmacologic and surgical interventions cannot be directly compared because of their inherent confounding by indication, we assess the comparative effectiveness of different options within both pharmacologic and surgical approaches.

We include both contextual and key questions. We systematically reviewed and assessed the risk of bias of the literature meeting our inclusion criteria for key questions, which address the comparative effectiveness of interventions. We provide a narrative review of relevant literature for contextual questions as few effectiveness studies address these questions, which are related to natural history of IH and markers for occult IH.

We anticipate this report will be of primary value to organizations that develop guidelines for managing IH, to clinicians who provide care for children with IH, and for families making treatment decisions. IH is diagnosed and treated by clinicians including pediatricians, dermatologists, otolaryngologists, family physicians, nurses, nurse-practitioners, physician assistants, hematologists, and general and plastic surgeons. This report supplies practitioners and researchers up-to-date information about the current state of evidence, and assesses the quality of studies that aim to determine the outcomes and safety of treatments for IH.

Key Questions

We developed Key Questions (KQs) and Contextual Questions (CQs) in consultation with Key Informants and the Task Order Officer. Questions were posted for review to the AHRQ Effective Health Care Web site. Questions were as follows:

CQ1. What is known about the natural history of infantile hemangiomas, by hemangioma site and subtype? What are the adverse outcomes of untreated infantile hemangiomas? What characteristics of the hemangioma (e.g., subtype, size, location, number of lesions) indicate risk of significant medical complications that would prompt immediate medical or surgical intervention?

CQ2. What is the evidence that five or more cutaneous hemangiomas are associated with an increased risk of occult hemangiomas?

KQ1. Among newborns, infants, and children up to 18 years of age with known or suspected infantile hemangiomas, what is the comparative effectiveness (benefits/harms) of various imaging modalities for identifying and characterizing hemangiomas?

a. Does the comparative effectiveness differ by location and subtype of the hemangioma?

KQ2. Among newborns, infants, and children up to 18 years of age with infantile hemangiomas who have been referred for pharmacologic intervention, what is the comparative effectiveness (benefits/harms) of corticosteroids or beta-blockers?

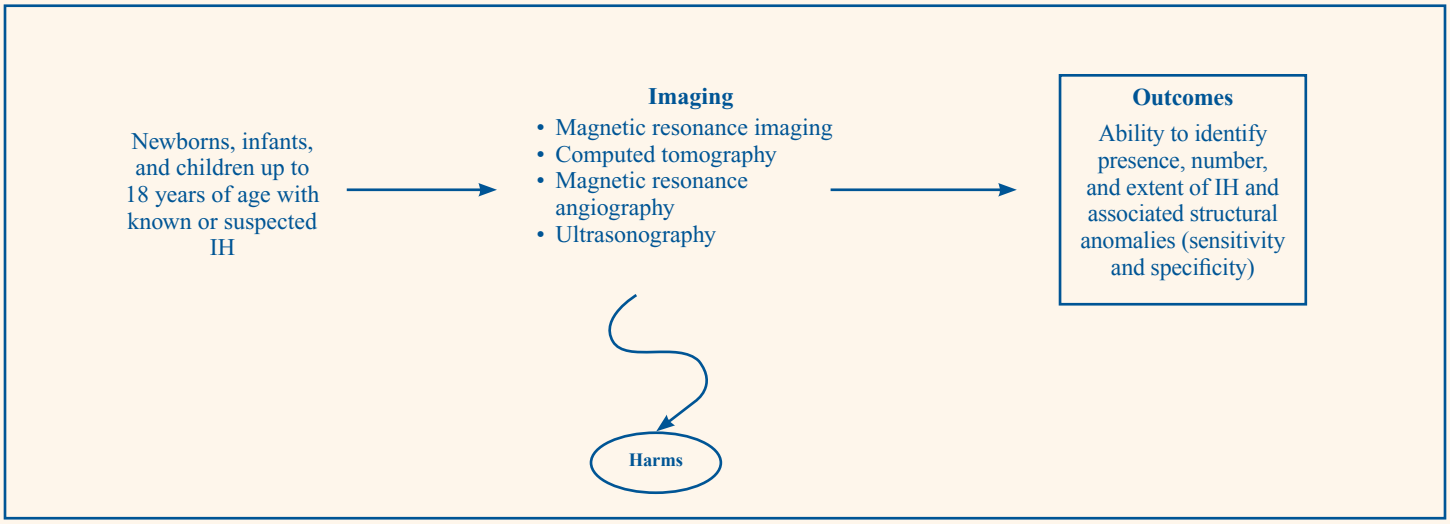
KQ3. Among newborns, infants, and children up to 18 years of age with infantile hemangiomas for whom treatment with corticosteroids or beta-blockers is unsuccessful what is the comparative effectiveness of second line therapies including immunomodulators and angiotensin-converting enzyme inhibitors?

KQ4. Among newborns, infants, and children up to 18 years of age with infantile hemangiomas who have been referred for surgical intervention, what is the comparative effectiveness (benefits/ harms) of various types of surgical interventions (including laser and resection)?

Analytic Framework

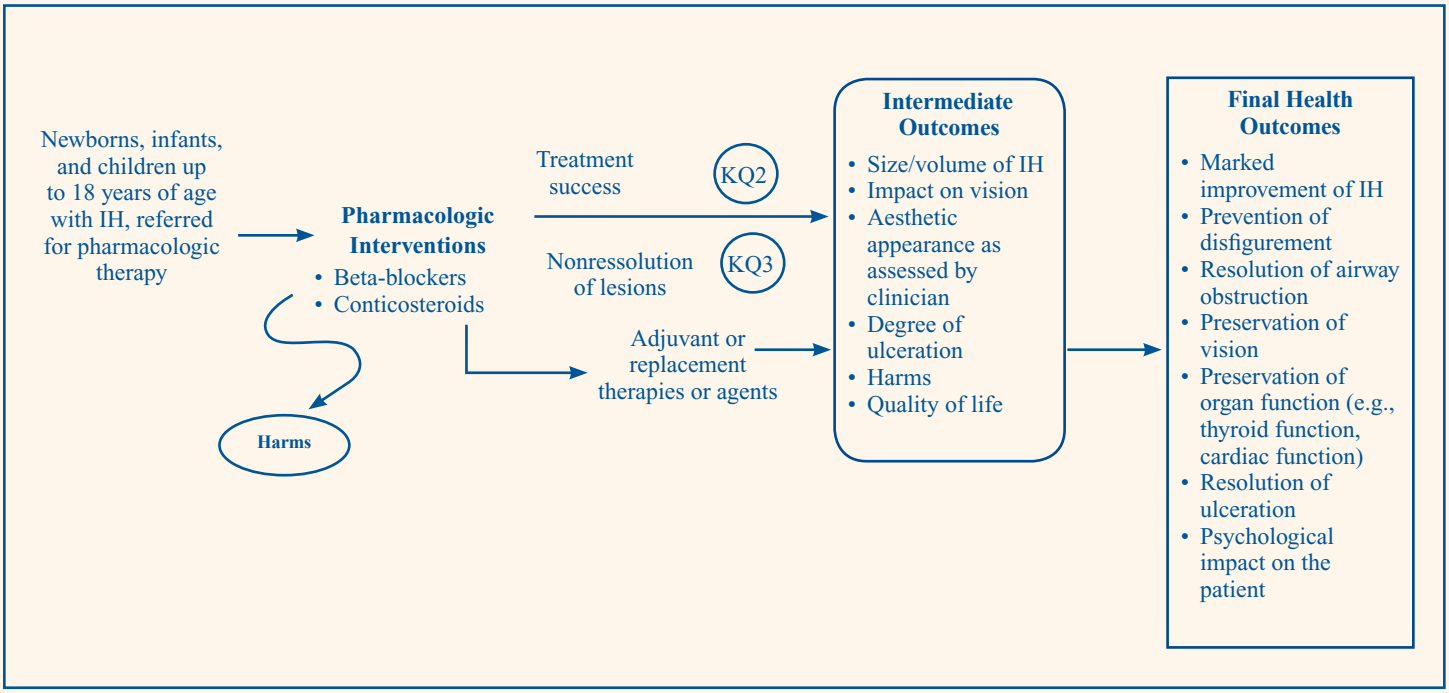
The analytic frameworks illustrate the population, interventions, and outcomes that guided the literature search and synthesis of comparative studies (Figures A-C). The frameworks depict the KQs within the context of the population, intervention, comparator, outcomes, timing, and setting (PICOTS) parameters described in the review. In general, the figures illustrate how imaging modalities or interventions such as magnetic resonance imaging (MRI), beta-blockers, or laser may result in intermediate outcomes such as change in hemangioma size or change in vision and/or in final health outcomes such as detection of hemangiomas for imaging modalities or resolution of hemangioma or changes in quality of life for medical or surgical treatments. Also, adverse events may occur at any point after imaging or receipt of the intervention.

Figure A. Analytic framework for KQ1



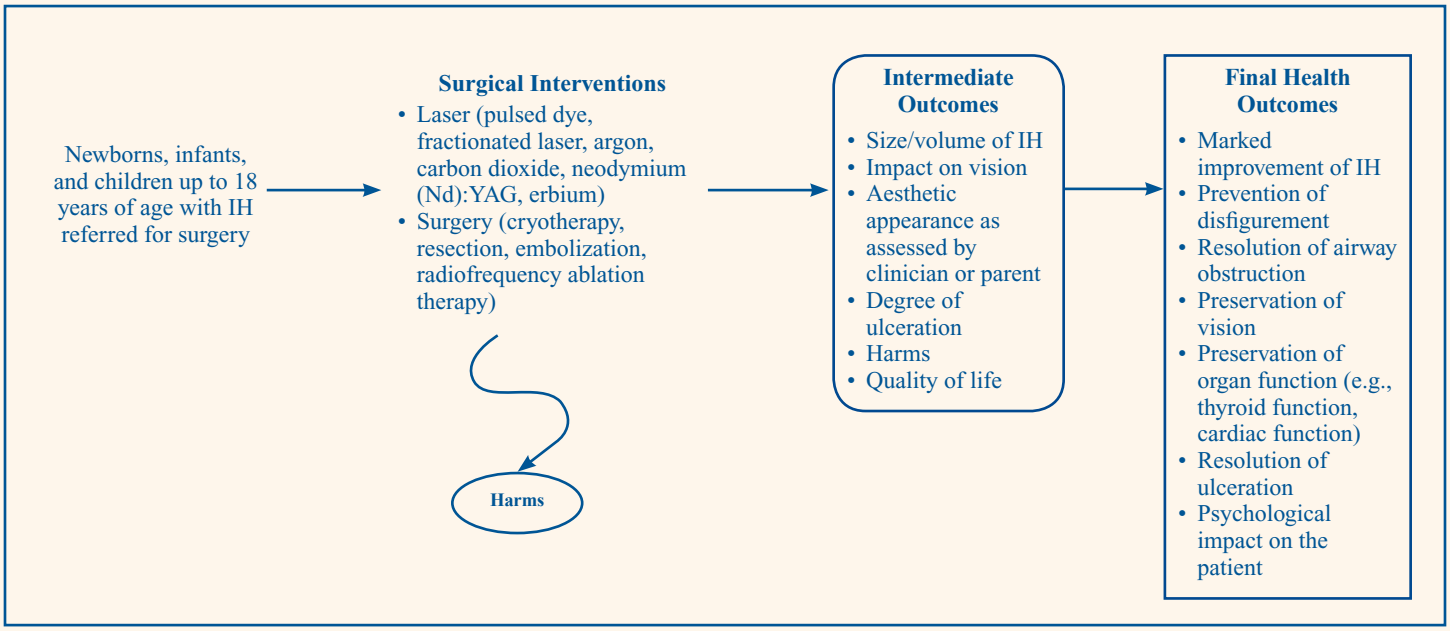
Abbreviations: IH = infantile hemangioma; KQ = Key Question

Figure B. Analytic framework for KQ2 and KQ3



Abbreviations: IH = infantile hemangioma; KQ = key question

Figure C. Analytic framework for KQ4



Abbreviations: IH = infantile hemangioma; KQ = key question; ND:YAG = Neodymium Yttrium Aluminum Garnet

Methods

Literature Search Strategy

A librarian employed search strategies (Appendix A of the full report) to retrieve research on diagnostic modalities, and interventions for IH. We searched MEDLINE® via the PubMed® interface, the Cumulative Index of Nursing and Allied Health Literature (CINAHL®), and Embase (Excerpta Medica Database). We limited searches to the English language and to studies published from 1982 to the present to reflect current standards of care and classification schema for IH.[20] We searched the same databases without date restrictions to identify contextual information. Our last search was conducted in June 2015. We manually searched reference lists of included studies and of recent narrative and systematic reviews and meta-analyses.

Inclusion and Exclusion Criteria

We developed criteria for inclusion and exclusion (Table A) in consultation with a Technical Expert Panel. We limited studies to those published in English. We also excluded studies evaluating multiple lesion types (e.g., cavernous hemangioma, hemangioblastoma, vascular malformations, noninvoluting congenital hemangiomas) unless we could clearly extract data pertaining to children with IH or if the majority of children had IH. To be included for KQ3, studies had to note explicitly that all children had received prior treatment with beta-blockers or steroids and were therefore receiving a second-line treatment. We also included case series with at least 25 children with IH to address harms, but not effectiveness. We selected the lower bound of 25 as a conservative value based on a preliminary review of case series.

Table A. Inclusion criteria

Category	Criteria
Study population	Newborns, infants, and children up to 18 years of age with infantile hemangiomas or suspected infantile hemangiomas
Publication languages	English only
Publication year	1966-present (CQ 1 and 2) 1982-present (KQ 1, 2, 3, 4)
Admissible evidence	Admissible designs Original research studies providing sufficient detail regarding methods and results to enable use and aggregation of the data and results Contextual Questions (CQ): • Systematic and non-systematic reviews, articles reporting on the history of IH diagnosis or treatment, practice guidelines, meta-analyses, RCTs, case series with at least 25 children with IH, and any comparative studies Comparative Effectiveness Key Questions (KQ): • Imaging accuracy: RCTs and any comparative studies • Benefits of interventions: RCTs and any comparative studies • Harms of interventions: RCTs, any comparative studies, and case series with at least 25 children with infantile hemangiomas
Other criteria	Studies must address one or more of the following: • Diagnostic imaging (e.g., magnetic resonance imaging, computed tomography, magnetic resonance angiography, echocardiography, ultrasound, endoscopy) • Surgical interventions (e.g., cryotherapy, resection, embolization, radiofrequency ablation therapy) or laser interventions (e.g., pulsed dye, fractionated laser, argon, carbon dioxide, neodymium (Nd): YAG, erbium) • Pharmacologic interventions (e.g., beta-blockers, corticosteroids, immunomodulators, immunosuppressants, angiotensin-converting enzyme inhibitors, antiangiogenic agents, antineoplastics)
Category	**Criteria**
Other criteria (continued)	• Data (including harms) related to diagnostic modalities or interventions for infantile hemangiomas for the following outcomes: **Imaging studies** – Ability to identify presence, number, and extent of hemangiomas and associated structural anomalies (sensitivity and specificity) – Harms **Surgical or pharmacologic intervention studies** – Size / volume of hemangioma – Impact on vision – Aesthetic appearance as assessed by clinician or parent – Degree of ulceration – Quality of life – Harms Relevant outcomes must be able to be abstracted from data in the papers Data must be presented in the aggregate (vs. individual participant data)

Abbreviations: CQ = contextual question, KQ = key question, Nd:YAG = neodymium yttrium aluminum garnet, RCT = randomized controlled trial

Study Selection

Two reviewers independently assessed each abstract. If one reviewer concluded that the article could be eligible to address a KQ based on the abstract, we retained it for review of the full text. Two reviewers independently assessed the full text of each included study potentially addressing a KQ, with any disagreements adjudicated by a senior reviewer. Reviewers could flag studies that potentially addressed a C Q identified in the screening process for KQs.

We also screened studies identified in our separate database searches for studies potentially addressing CQs. We did not conduct dual screening of studies identified in our searches for CQs. If one reviewer determined that a study could be eligible, we assessed its relevance to the CQs. Excluded studies had no further analysis.

Data Extraction and Synthesis

We extracted data from included studies into templates that recorded study design, descriptions of the study population (for applicability), description of the interventions, and baseline and outcome data on constructs of interest. Data were initially extracted by one team member and reviewed for accuracy by a second. Extracted data for KQs are available in the Systematic Review Data Repository.

We summarized data for KQs qualitatively using summary tables where meta-analyses were not possible. We provided a narrative summary of relevant papers for CQs.

We identified sufficient data to address the effectiveness of pharmacologic interventions using quantitative meta-analysis methods. Studies were included in the meta-analysis subset provided that they satisfied the following additional inclusion criteria:

- Outcomes were reported quantitatively, using an objective metric for reporting intervention effects that could be converted into a proportion of IH clearance.
- One or more study arms evaluated a single intervention; study arms in which two or more treatments were applied were excluded.
- Reported outcomes were accompanied by an associated measure of variation or precision.
- Non-control pharmacologic treatments could be reasonably classified into one of the following classes of agents: oral, intralesional, or topical propranolol; intralesional triamcinolone; topical or ophthalmic timolol; and oral steroid.
- Studies evaluated IH in multiple locations (vs. specific anatomic areas) as most studies included IH in multiple areas.

In addition to the diverse suite of interventions, outcomes were reported in a variety of ways. Most identified an arbitrary threshold of IH clearance (e.g., >75%) as a positive outcome, or divided the continuous clearance measure into a small number of categories. Others reported visual analog scale scores or other measures. In order to incorporate as many quality studies as possible, we constructed a Bayesian latent variable model. This model allowed several different types of outcome data and a suite of pharmacologic interventions to be analyzed in the same model. The estimands of interest were the expected proportion of clearance of IH associated with each intervention agent (i.e., with a mean expected clearance rate of 80% for a given agent, we would expect to see, on average, 80% clearance of IH in a child receiving that agent), along with associated posterior uncertainty. A full description of the meta-analytic methods is reported in Appendix D of the full report.

Quality (Risk-of-Bias) Assessment of Individual Studies

We used separate tools appropriate for specific study designs to assess quality of individual studies addressing KQs: questions adapted from the RTI item bank to assess RCTs,[21] the Newcastle-Ottawa Quality Assessment Scale for cohort studies,[22] the QUADAS tool for diagnostic imaging studies,[23] and a tool adapted from questions outlined in the RTI item bank and the McMaster McHarms tool to assess reporting of harms.[24] Appendix B of the full report includes questions used in each tool.

Two team members independently assessed each included study, with discrepancies resolved through discussion to reach consensus and/or adjudication by a senior reviewer. The results of these assessments were then translated to the Agency for Healthcare Research and Quality standard of "good," "fair," and "poor" quality designations, as described in the full report. Quality ratings for each study are in Appendix F of the full report.

Strength of the Body of Evidence

Two senior investigators graded the strength of the evidence (SOE) for key intervention/outcome pairs (i.e., the final outcomes listed in Figures A-C) using methods based on the "Methods Guide for Effectiveness and Comparative Effectiveness Reviews."[25] We assessed the domains of study limitations (low, medium, high level

of limitation), consistency (inconsistency not present, inconsistency present, unknown), directness (direct, indirect), precision (precise, imprecise), and reporting bias. We did not assess SOE for contextual questions. The team reviewed the final SOE designation. The possible grades were:

- High: High confidence that the evidence reflects the true effect. Further research is unlikely to change estimates.
- Moderate: Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of effect and may change the estimate.
- Low: Low confidence that the evidence reflects the true effect. Further research is likely to change confidence in the estimate of effect and is also likely to change the estimate.
- Insufficient: Evidence is either unavailable or does not permit a conclusion.

We assessed the SOE for the KQs only.

Applicability

We assessed the applicability of findings reported in the included literature addressing KQs to the general population of children with IH by determining the population, intervention, comparator, and setting in each study and developing an overview of these elements for each intervention category. We anticipated that areas in which applicability would be especially important to describe would include the diagnostic criteria for IH, age at treatment initiation, and the anatomic location and morphology of IH. Applicability tables for each intervention are in Appendix G of the full report.

Results

CQs

We included 68 studies in the narrative summary of information addressing CQ. The literature identified to answer contextual questions suggested that indications for referral include large size; segmental type; risk for complications including bleeding, ulceration, and pain; involvement of critical structures; and risk factors for occult lesions (numerous cutaneous lesions, beard distribution). Further, the potential for psychosocial concerns may support referral for patients with uncomplicated lesions in highly visible areas on a case-by-case basis.

Overall, limited literature addressed the association of a higher number of cutaneous IH and extracutaneous IH. Some data from case series suggested support for a higher index of suspicion in children with multiple lesions or with facial lesions in a beard distribution. Studies have primarily assessed associations between cutaneous IH and hepatic IH and cutaneous facial IH and airway IH.

Comparative Effectiveness Questions

Article Selection and Overview

We identified 4132 nonduplicative titles or abstracts with potential relevance, with 2859 proceeding to full text review. We included 148 unique studies (153 publications) in the review. These 148 studies included 42 comparative studies, 38 addressing effectiveness and harms of therapies and 4 assessing effectiveness only, and 106 case series providing data on harms only. The 148 unique studies addressing KQs comprise 15 randomized controlled trials (RCTs), 5 prospective and 19 retrospective cohort studies, 2 diagnostic accuracy studies (defined as studies that compared the accuracy of imaging modalities in identifying or characterizing infantile hemangioma [IH]), 1 prospective comparative study that used an untreated IH as a control, and 106 case series (used for harms data only).

We considered 6 of these comparative studies to be good quality, 22 fair quality, and 14 poor quality. One-hundred and forty-four studies (comparative studies and case series) reported harms/adverse events data. We considered 14 of these as good quality for harms reporting, 3 as fair quality for harms reporting, and the remainder (n=127) as poor quality for harms reporting.

KQ1. Effectiveness and Harms of Imaging Modalities for IH

Two poor quality diagnostic accuracy studies addressed imaging modalities.[26,27] Studies assessed IH in different anatomic locations and reported differing findings for the sensitivity of ultrasound and effectiveness of imaging modalities depending on location or subtype. In one comparing magnetic resonance imaging (MRI) and ultrasound for imaging spinal anomalies (n=48), ultrasound had a sensitivity of 50 percent (95% CI: 18.7% to 81.3%) and specificity of 77.8 percent (95% CI: 40% to 97.2%) for identifying anomalies including tethered cords and intraspinal IH. We calculated the sensitivity of both modalities for identifying intraspinal hemangioma specifically: assuming a false positive value of 0, ultrasound had a sensitivity of 20 percent (95% CI: 3.30% to 71.19%), and the sensitivity of MRI was 100 percent (95% CI: 66.21% to 100%). In another study, ultrasound identified hepatic IH in 42 of 44 patients

(sensitivity of 95%). Overall, studies were limited by the size of cohorts, lack of standard processes, and lack of direct comparison at the same time point using the various imaging modalities. We considered the SOE for all imaging modalities to be insufficient given single, small studies addressing different approaches, using weaker study designs and precluding a meta-analysis. The studies did not address harms.

KQ2. Effectiveness and Harms of Corticosteroids and Beta-Blockers

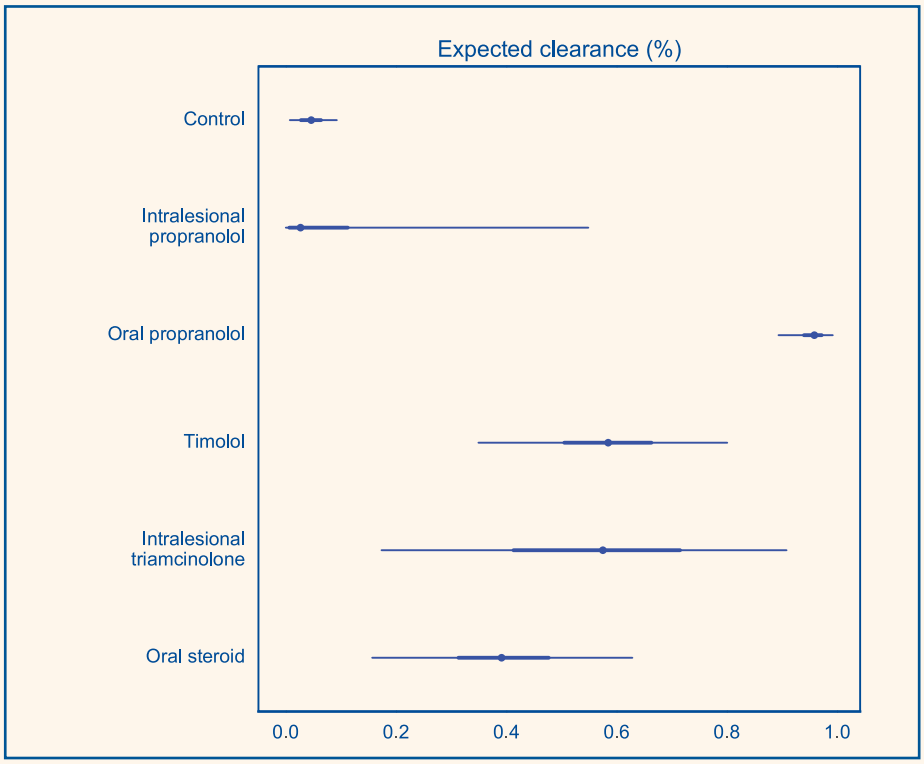
Summary of Meta-Analysis Results

We included 18 studies in a network meta-analysis. All studies addressed pharmacologic agents and included five RCTs and four cohort studies evaluating oral propranolol and placebo or observation or another active agent; one RCT and one cohort study comparing oral propranolol and other oral beta-blockers; three cohort studies and two RCTs assessing topical timolol compared with placebo or observation or another agent; and one RCT and one cohort study evaluating different steroids. Four studies were good quality; nine were fair quality; and five were poor quality. Studies included a total of 1265 children with IH.

In our network meta-analysis, oral propranolol had the highest clearance rate (Figure D). As described in the qualitative results, there were substantially more studies of oral propranolol available for inclusion in the analysis. The expected efficacy of control arms was estimated to be 6 percent (95% Bayesian credible interval [BCI]: 1% to 11%), and all non-control treatments were estimated to have a larger expected clearance than control arms. As noted, the largest mean estimate of expected clearance was for oral propranolol (95%, 95% BCI: 88% to 99%), followed by topical timolol (62%, 95% BCI: 39% to 83%), and intralesional triamcinolone (58%, 95% BCI: 21% to 93%). Oral steroids had a rate of 43 percent (95% BCI: 21% to 66%).

The variation in treatment outcomes was high in beta-blocker studies. Thus, the potential for greater clearance was much higher in patients treated with oral propranolol, but the variability in outcomes makes it difficult to anticipate the likely outcome for a given patient. As noted, corticosteroid treatment demonstrated lower overall effectiveness.

Figure D. Estimates of expected IH clearance



Note: Estimates of expected IH clearance are expressed as percent clearance relative to initial condition for each treatment, along with associated posterior interquartile range (thick lines) and 95% credible interval (thin lines).

To assess for methodologic heterogeneity, we ran additional models with only RCTs and with only good and fair quality studies. Estimates did not differ markedly when poor quality studies were removed, though BCI typically widened; thus, we report the model with poor quality studies included. To examine the possible effect of bias due to the inclusion of cohort studies, we fit the same model to RCT studies only. The resulting estimates were similar to those of the model fit to all studies, but with much wider posterior credible intervals. Since there was no obvious systematic bias due to study design, we reported the model estimates based on the entire body of evidence.

Corticosteroids

We identified 24 studies (three RCTs, one cohort study, and 20 case series) reporting outcomes and/or harms following corticosteroid use in children with IH. Comparative studies included a total of 239 children, and case series included 3508. We considered one RCT as good, one as fair, and one as poor quality and the cohort study as fair quality. We rated all case series as poor quality for harms reporting. Steroids studied varied in dose, type, and route of administration, and the ages of children included in comparative studies ranged widely from 1 to 72 months. IH size was reduced significantly in the oral prednisolone arm compared with intravenous methylprednisolone arm in one RCT.

More children in treatment arms than in an observation arm in another RCT comparing oral prednisolone, intralesional triamcinolone, and conservative management had at least a 50 percent reduction in lesion size. More children receiving intralesional triamcinolone than topical mometasone in a third RCT had an excellent response, but the study did not provide statistical comparisons. Lesion reduction did not differ among children receiving different doses of prednisolone or methylprednisolone in a cohort study. Of the 219 children who received steroids in three comparative studies reporting such data, 140 had a "good" or "fair" response to steroids. One study reported that 92 of 238 children who underwent observation only had complete or near complete regression of IH at a median of 2 years of followup. In our network meta-analysis, oral steroids had a mean estimated expected clearance rate of 43 percent (95% BCI: 21% to 66%) and intralesional triamcinolone had a rate of 58 percent with wide confidence boundaries (95% BCI: 22% to 93%). Overall, SOE is moderate for the effect of oral steroids on clearance rates and low SOE for intralesional steroids to have a modest (albeit larger) effect relative to control, with wide confidence bounds.

Harms were varied and frequently included Cushingoid facies, irritability/mood changes, growth retardation, and skin atrophy or depigmentation. Studies typically did not explicitly report terminations due to adverse events, although one study of oral prednisolone noted discontinuation of the drug in 1 of 10 participants due to vomiting. Another comparing prednisolone (n=8) and propranolol (n=11) reported five discontinuations in the steroid arm due to growth or endocrine changes. Study enrollment was stopped due to adverse events. Overall, steroids were consistently associated with clinically important harms that may be important in making treatment decisions. The SOE is moderate for the association of steroids with clinically important harms.

Beta-Blockers

Eighty-one studies (25 comparative studies and 56 case series) evaluated propranolol (oral, topical, intralesional), oral nadolol, oral atenolol, or timolol (gel or ophthalmic solution). Beta-blockers typically demonstrated significantly greater effects on reducing lesion size or volume than did control or other active comparators. Compared with a mean estimated expected clearance rate of 6 percent (95% BCI: 1% to 11%) in placebo or observation arms, oral propranolol had a rate of 95 percent (95% BCI: 88% to 99%). We summarize effectiveness results by comparator below.

Harms most frequently reported with beta-blockers included hypotension, hypoglycemia, bradycardia, sleep disturbances, cold extremities, gastrointestinal symptoms, and bronchial irritation (classified as hyperreactivity, bronchospasm, bronchiolitis, and cold induced wheezing; moderate SOE association of propranolol with clinically important and minor harms). Harms generally did not cause treatment discontinuation (n=40/2541 [1.6%] children in case series and no children in comparative studies).

Propranolol versus observation or placebo. We identified four studies (two good and one fair quality RCTs and one fair quality cohort study) evaluating propranolol versus placebo or observation. Propranolol was associated with significantly greater clearance of IH compared with the control arm in all four studies. In the largest RCT, which included 456 children without problematic IH receiving up to 3 mg/kg/day of propranolol, 60 percent of children in the propranolol group had complete or near complete resolution of IH after 24 weeks of treatment compared with 4 percent in the placebo group. The recommended dose of propranolol in this IH population remains to be determined, but the majority of studies to

date have investigated the 2 mg/kg/day dosing regimen. Despite changes in lesion size in many children receiving propranolol, some children do not appear to respond to propranolol, but these children are not well-characterized to date.

In network meta-analysis, the mean expected clearance rate for oral propranolol was 95 percent (95% BCI: 88% to 99%) relative to 6 percent for placebo/observation arms (95% BCI: 1% to 11%); IH size reductions were greater in propranolol arms versus control in all individual studies, thus we considered the SOE as high for greater effectiveness of propranolol compared with placebo or observation based on individual comparisons and the meta-analysis.

Propranolol versus other active modalities. Ten studies compared propranolol to another modality including steroids, pulse dye laser (PDL), bleomycin, or historical treatments. Studies comparing propranolol and steroids to reduce IH size had conflicting findings. Propranolol was more effective than steroids in three studies, while two others studies did not find effectiveness differed significantly between these treatments. In network meta-analysis, pooling data from multiple studies, propranolol was superior to oral steroids (95% clearance [95% BCI: 88% to 99%]) versus 43% clearance [95% BCI: 22% to 66%]). These combined effects from individual studies and meta-analysis conferred moderate SOE for superiority of propranolol over steroids at achieving clearance.

One additional retrospective cohort study assessing only vision outcomes reported no significant differences between oral propranolol and intralesional steroids in improving amblyopia, but children in the propranolol arm had a significantly shorter duration of therapy ($p<.001$) and required fewer additional treatments than those receiving steroids (p=NS).

Another retrospective study found that PDL therapy either in conjunction with or subsequent to propranolol therapy is more effective than propranolol alone. Another study found the likelihood of laser treatment was lower in participants treated with propranolol than participants who did not receive the medication. The study that compared propranolol with bleomycin did not demonstrate that one intervention was more effective than the other. In a final study, ulcerated lesions healed more quickly with propranolol than with other treatments including laser.

Oral propranolol versus other beta-blockers or dosage forms. Three small studies compared propranolol with nadolol or atenolol and one study evaluated oral, intralesional, and topical propranolol. Atenolol and nadolol demonstrated promising effects on lesion size (little difference in effectiveness of propranolol and atenolol and greater effectiveness of nadolol in a small study comparing nadolol and propranolol) and low levels of adverse effects, which may suggest that improvements can be achieved in the propranolol safety profile. More children receiving oral propranolol had an excellent or good level of resolution than those receiving topical or intralesional propranolol (n=11/15, 8/15, 5/15, respectively), but the difference among groups was not significant.

In head-to-head comparisons, there were no significant differences in response between propranolol and atenolol in two studies and better response to nadolol versus propranolol in one small study. We considered the SOE as low for no difference in response with propranolol, nadolol, or atenolol (systemic beta-blockers).

Timolol versus placebo/observation or other active modality. Six comparative studies addressed timolol (two RCTs and four cohort studies). All studies included children with superficial IH, and two (one comparing timolol with observation and one comparing timolol and laser) also included children with mixed (superficial and deep) IH. Timolol was significantly more effective than observation or placebo in three studies, and one study comparing topical imiquimod with timolol did not demonstrate that one intervention was more effective than the other. In one study comparing timolol and PDL+Nd:YAG laser, timolol was associated with greater improvements in superficial lesions, while laser was associated with greater improvements in mixed (superficial and deep) lesions. In another comparing timolol alone with timolol plus PDL, mean global assessment scores were more improved in the combination arm than in the timolol arm, though IH in 97 percent of children in both arms improved from baseline. No harms of timolol were observed in any study.

In network meta-analysis, the mean expected clearance rate for topical timolol was 62 percent (95% BCI: 39% to 83%) relative to 6 percent (95% BCI: 1% to 11%) for placebo or observation arms. We considered SOE as low for the effectiveness of timolol compared with placebo or observation.

KQ3. Effectiveness and Harms of Second-Line Therapies Following Beta-Blockers or Corticosteroids

We did not identify any studies addressing this question.

KQ4. Effectiveness and Harms of Surgical Interventions

Studies of Laser Treatment

Eleven comparative studies (three RCTs and seven retrospective and one prospective studies including a total of 1029 children) and 30 case series (n=3831) addressed surgical approaches. We considered one RCT as good, two RCTs and two cohort studies as fair, and the remainder of studies as poor quality.

Most comparative studies were small (≤55 participants), but one RCT and three retrospective cohort studies included more than 120 children. Lasers varied across studies in type, pulse width, or cooling materials. Most studies assessed variations of PDL (n=7) and examined heterogeneous endpoints. Most studies reported on treatment of cutaneous lesions. Several studies used historical controls, based on now superseded treatment regimens.

In two RCTs reporting level of clearance, at least 40 percent of children in laser or observation arms had complete or near complete clearance of IH. RCTs included younger children with lesions likely in the proliferative phase. One reported no differences in level of reduction between traditional and longer pulse PDL. Cohort studies assessed outcomes after carbon dioxide and Nd:YAG (neodymium yttrium aluminum garnet) lasers and typically reported some resolution of lesion size, but heterogeneity among studies limits our abilities to draw conclusions.

Overall, longer pulse PDL with epidermal cooling was the most commonly used laser for cutaneous lesions and Nd:YAG was the most commonly used intralesionally. Most studies reported a higher success rate with longer pulse PDL compared to observation in managing the size of IH, although the magnitude of effect differed substantially. CO2 laser was used for subglottic IH in a single study, and was noted to have a higher success rate and lower complication rate than both Nd:YAG and observation.

Two comparative studies addressed surgical approaches (cryotherapy, intense pulsed light photothermolysis, sclerosis) and reported some positive effects in reducing IH size or improving appearance, but their smaller size and low quality preclude conclusions (insufficient SOE). Strength of evidence for outcomes after surgical treatments ranged from insufficient to low for effectiveness outcomes. The evidence was limited by low sample size, lack of comparisons of the same modalities, and variations in the laser settings used including wavelength and cooling protocols. For Nd:YAG and CO2 lasers, cryotherapy, and intense pulsed light photothermolysis, all studies were severely limited by sample size, and SOE was determined to be insufficient in all outcome parameters.

Harms associated with laser treatment included skin atrophy, bleeding, scarring, ulceration purpura, and pigmentation changes. Bleeding and ulceration were observed in the immediate postoperative period, distinguishing these complications from the possible natural complications of IH themselves. Overall, we considered SOE to be moderate for pigmentation changes with PDL, which was most frequently hypopigmentation. SOE was low for bleeding in the immediate postoperative period. Due to low sample size and limitations in reporting, pain and scarring were found to have insufficient SOE. For Nd:YAG lasers, evaluation for scarring was most frequently reported, and there was low SOE to support no difference in scarring between Nd:YAG and observation. Evidence was deemed insufficient to comment on pigmentation changes and bleeding for children treated with Nd:YAG.

Studies of Surgical Treatment

Few comparative studies addressed surgical approaches. Two comparative studies addressed cryotherapy versusno treatment and intense pulsed light photothermolysis with or without sclerotherapy versus cryotherapy and reported improvements in IH but included few participants in each arm (total n=263).

Most surgical case series (n=13) were retrospective and included a total of 838 children. We considered all to be poor quality for harms reporting and insufficient SOE for association with any harms. Frequently reported harms included scarring and wound dehiscence.

Discussion

Key Findings From CQs

The literature identified to answer contextual questions described a broader range of indications for referral of patients with IH and suggested support for a higher index of suspicion of extracutaneous IH in children with multiple cutaneous lesions or with facial lesions in a beard distribution. Studies have primarily assessed associations between cutaneous IH and hepatic IH and cutaneous facial IH and airway IH.

Key Findings and Strength of Evidence for KQs

Until fairly recently, corticosteroids were the treatment of choice for IH. As reported in this review, corticosteroids

demonstrate moderate effectiveness but may be associated with clinically important side effects. More recently, beta-blockers, and propranolol specifically, have been studied and recommended for use. Studies of propranolol have compared its effectiveness to placebo or observation arms, to corticosteroids and other modalities, and to other beta-blockers. Relative to observation or placebo, propranolol has been consistently shown to be superior in individual studies and in our meta-analysis. Relative to other modalities, including steroids and bleomycin, we find that propranolol is generally superior. In two studies comparing steroids and propranolol, however, differences in reduction of lesion size were not significantly different between groups. Finally, given that propranolol has been demonstrated to be associated with positive outcomes, the question of whether effectiveness is associated with propranolol specifically or beta-blockers in general has been studied. Although there are only three small studies available, they suggest that other beta-blockers may also confer positive effects, potentially with fewer side effects, but these findings are preliminary. Studies of the beta-blocker timolol, used as a topical gel or solution, also reported greater effectiveness for timolol compared with placebo/observation in reducing IH lesion size and no differences in effects in one study comparing ophthalmic timolol and imiquimod.

In our network meta-analysis, propranolol had the highest clearance rate, with high variability. The preponderance of available evidence used in the meta-analysis was derived from studies of propranolol and corticosteroids.

In terms of surgical interventions, only laser has been adequately studied. Most studies focused on PDL and generally it was found to be more effective than other types of laser, but effects remain unclear as studies were significantly heterogeneous, and the role of laser vis-a-vis beta-blockers is not clearly described in the literature. Data are inadequate to address the role of imaging in guiding treatment.

We assessed strength of evidence for the effectiveness and harms of interventions using the qualitative and quantitative approaches described fully in the Methods section of the full report. Overall, the evidence to answer KQs about interventions for children with IH ranged from insufficient to moderate when the comparisons are made with the individual studies qualitatively. The network meta-analysis provided additional data. We assessed strength of evidence separately for the predicted outcomes of the meta-analysis and key direct comparisons available in the literature (Tables B-D).

Imaging. Studies of imaging modalities addressed different approaches and different anatomic locations (intraspinal, hepatic IH). The sensitivity of ultrasound in these two small studies ranged from 20 percent to 95 percent. Sensitivity of MRI was 100 percent in one study. Findings are limited by the size of cohorts, lack of standard processes, and lack of direct comparison at the same time point using the various imaging modalities.

We considered the strength of evidence for all imaging modalities to be insufficient given single, small studies addressing different approaches, using weaker study designs and precluding a meta-analysis (Table B). The studies did not address harms.

Corticosteroids. Studies of corticosteroids similarly evaluated different steroids, routes of administration, and comparators. Children in treatment arms in individual studies typically had modest improvement in lesion size. In our network meta-analysis, oral steroids had a mean estimated expected clearance rate of 43 percent (95% BCI: 21% to 66%), and intralesional triamcinolone had a rate of 58 percent (95% BCI: 22% to 93%) but with wide confidence bounds.

Studies of steroids assessed multiple agents, and we combined these in the meta-analysis into oral and intralesional groupings. Thus, while strength of evidence is insufficient on the basis of qualitative analysis of single studies of individual agents compared to one another, strength of evidence is moderate for the effect of oral steroids on clearance rates and low strength of evidence for intralesional steroids to have a modest (albeit larger) effect relative to control with wide confidence bounds. Steroids were consistently associated with clinically important harms including Cushingoid appearance, infection, growth retardation, hypertension, and mood changes. We considered the strength of evidence to be moderate for the association of steroids with these clinically important harms (Table C).

Beta-blockers. Studies of beta-blockers typically reported significantly greater resolution of IH in beta-blocker arms compared with placebo/observation or other active agents. Compared with a mean estimated expected clearance rate of 6 percent (95% BCI: 1% to 11%) in placebo or observation arms and 43 percent (95% BCI: 21% to 66%) for oral steroids, the mean estimated clearance rate for oral propranolol was much higher (95%, BCI: 88% to 99%) in our network meta-analysis.

In individual comparative studies, propranolol at doses of 2 to 3 mg/kg/day administered for 6 months promoted lesion regression with few serious side effects in children with IH. While the majority of studies investigated propranolol at a total of 2 mg/kg/day, one RCT with the largest number of patients utilized a treatment of 3 mg/kg/day. The recommended dose of propranolol in this IH population remains to be determined, but the majority of studies to date have investigated the 2 mg/kg/day dosing regimen. Despite changes in lesion size in many children receiving propranolol, a percentage of patients do not appear to respond to propranolol, but these children are not well-characterized to date.

Other oral beta-blockers (atenolol, nadolol) in small studies demonstrated promising effects on reducing lesion size and few adverse effects, which may suggest that improvements can be achieved in the propranolol safety profile. Harms most frequently reported with use of oral beta-blockers (propranolol, atenolol, nadolol) included sleep disturbances, cold extremities, gastrointestinal symptoms, bronchial irritation (classified as hyperreactivity, bronchospasm, bronchiolitis, cold induced wheezing), and decreases in blood pressure or heart rate.

In studies comparing propranolol with other active comparators including steroids, PDL, bleomycin, or historical treatments, findings were inconsistent, with two studies reporting greater effectiveness for propranolol compared with steroids and two noting no significant differences between propranolol and steroids. In network meta-analysis, oral propranolol was associated with a mean estimate of expected clearance of IH of 95 percent (95% BCI: 88% to 99%) compared with a lower rate for oral steroids of 43 percent (95% BCI: 21% to 66%). One study reported greater effectiveness for propranolol plus laser than propranolol alone. Another study found the likelihood of subsequent laser treatment was lower in participants treated with propranolol than participants who received other treatments. A study that compared propranolol with bleomycin did not demonstrate that one intervention was more effective than the other.

Studies of the topical beta-blocker timolol reported significantly greater resolution in treatment groups compared with placebo or observation, and one study reported no differences when compared with imiquimod. In network meta-analysis, the mean expected clearance rate for topical timolol was 62 percent (95% BCI: 39% to 83%).

With adequate data and good precision, we considered the strength of evidence to be high for the effect of propranolol on lesion size relative to observation or placebo. Individual studies assessed qualitatively also demonstrated greater effectiveness for propranolol compared with other active treatments.

Other oral beta-blockers have demonstrated promising effectiveness; we considered the strength of evidence to be low for no difference in response to propranolol and nadolol or atenolol based on three small studies. We considered strength of evidence to be low for greater effectiveness of topical timolol compared with observation or placebo. We considered the strength of evidence to be moderate for the association of propranolol with significant and minor harms (Table C).

Surgical approaches. Lasers studied varied across studies in type, pulse width, or cooling materials. Most studies assessed variations of PDL and examined heterogeneous endpoints. Heterogeneity among studies limits our abilities to draw conclusions. Multiple variations in treatment protocols did not allow for demonstration of superiority of a single laser method.

Harms associated with laser treatment included skin atrophy, bleeding, scarring, ulceration purpura, and pigmentation changes. Surgical harms included wound dehiscence.

Strength of evidence for outcomes after laser treatments ranged from insufficient to low for effectiveness outcomes (Table D). The evidence was limited by low sample size, and variations in the laser settings used including wavelength and cooling protocols. For Nd:YAG and carbon dioxide lasers, all studies were severely limited by sample size, and strength of evidence was determined to be insufficient in all outcome parameters. For harms, we considered the strength of evidence as moderate for pigmentation changes with PDL, which was most frequently hypopigmentation and strength of evidence as low for bleeding in the immediate postoperative period. Due to low sample size and limitations in reporting, pain and scarring were found to have insufficient strength of evidence. For Nd:YAG lasers, evaluation for scarring was most frequently reported, and there was low strength of evidence to support no difference in scarring between Nd:YAG and observation. Evidence was deemed insufficient to comment on pigmentation changes and bleeding for children treated with Nd:YAG and for any harms associated with other surgical approaches.

Table B. Summary of evidence in studies addressing effectiveness of imaging modalities

Intervention Type/ Number of Studies (Total N Participants)	Key Outcome(s)	Strength of Evidence (SOE) Grade	Findings
MRI vs. Ultrasound Cohort studies: 1 (48)	Accuracy in detecting spinal anomalies	Insufficient	Ultrasound had a sensitivity of 50% for identifying spinal anomalies including but not limited to IH and 20% for identifying intraspinal IH only compared with 100% for MRI. Insufficient SOE due to single small study with high study limitations.
MRI vs. Ultrasound vs. CT Cohort studies: 1 (55)	Accuracy in detecting liver IH	Insufficient	Ultrasound detected lesions in 42/44 children (95% sensitivity). Insufficient SOE due to single small study with high study limitations.

Abbreviations: CT = computed tomography; IH = infantile hemangioma; MRI = magnetic resonance imaging; RCT = randomized controlled trial; SOE = strength of evidence

Table C. Summary of evidence in studies addressing effectiveness of pharmacologic interventions

Intervention Type/ Number of Studies (Total N Participants)	Key Outcome(s)	Strength of Evidence (SOE) Grade	Findings
Steriods			
Oral steroids vs. Observation or Placebo Network meta-analysis	Improvement in IH	Moderate	In network meta-analysis oral steroids had a mean expected clearance rate of 43% (95% BCI: 21%-66%) compared with 6% (95% BCI: 1%-11%) for placebo/ observation arms. Moderate SOE for greater effectiveness of oral steroids vs. placebo/observation given low precision and high study limitations.
Intralesional Steroids vs. Observation or Placebo Network meta-analysis	Improvement in IH	Low	In network meta-analysis intralesional steroids had a mean expected clearance rate of 58% (95% BCI: 22%-93%) compared with 6% (95% BCI: 1%-11%) for placebo/observation arms. Low SOE for greater effectiveness of intralesional steroids vs. placebo/observation given relatively small numbers of participants contributing to this comparison and low precision.
All steroids RCT: 3 (138) Cohort studies: 3 (179) Case series: 10 (2974)	Clinically important harms (Cushingoid facies, growth retardation, mood changes /irritability, hypertension, infection)	Moderate	Comparative studies, case series, and package insert data consistently reported these adverse effects. Moderate SOE for association of steroids with clinically important harms due to high study limitations.

Table C. Summary of evidence in studies addressing effectiveness of pharmacologic interventions (continued)

Intervention Type/ Number of Studies (Total N Participants)	Key Outcome(s)	Strength of Evidence (SOE) Grade	Findings
Beta-Blockers			
Oral propranolol vs. Placebo or Observation Network meta-analysis RCT: 3 (510) Cohort studies: 1 (45)	Improvement in IH	High	In network meta-analysis, the mean expected clearance rate for oral propranolol was 95% (95% BCI: 88%-99%) relative to 6% (95% BCI: 1%-11%) for placebo/observation arms; greater reductions in IH size in propranolol arms vs. control in all individual studies. High SOE for greater effectiveness of propranolol vs. placebo or observation based on individual comparisons and the meta-analysis.
Propranolol vs. Placebo or Observation RCT: 1 (456) Cohort studies: 1 (45)	Rebound growth/ Need for further treatment	Moderate	Fewer than 15% of children in treatment arms had rebound growth or required longer/additional treatment. Moderate SOE for low level of rebound growth/need for further treatment associated with propranolol given few studies addressing the outcome.
Propranolol vs. Steroids Network meta-analysis RCT: 1 (19) Cohort studies: 4 (216)	Improvement in IH	Moderate	In head-to-head comparisons, propranolol more effective than steroids in 3 studies; 2 other studies reported no significant difference between oral or intralesional propranolol and oral or intralesional steroids. In network meta-analysis, pooling data from multiple studies, propranolol was superior to oral steroids (95% [95% BCI: 88% to 99%] clearance versus 43% [95% BCI: 21% to 66%] clearance). Moderate SOE for superiority of propranolol over steroids at achieving clearance based on combined effects from individual studies and network meta-analysis, high study limitations, and inconsistency.
Propranolol vs. Steroids Cohort studies: 1 (43)	Amblyopia	Insufficient	No significant difference in level of amblyopia between oral propranolol and intralesional triamcinolone arms in one small study. Insufficient SOE due to single study with high limitations.
Oral propranolol + prednisolone vs. Prednisolone vs. Propranolol alone RCT: 1 (30)	Improvement in IH	Insufficient	Significant size reductions from baseline in propranolol and combined arms (p values<0.01) but not in prednisolone arm in one small study. Insufficient SOE due to single study with high limitations.

Table C. Summary of evidence in studies addressing effectiveness of pharmacologic interventions (continued)

Intervention Type/ Number of Studies (Total N Participants)	Key Outcome(s)	Strength of Evidence (SOE) Grade	Findings
Oral propranolol vs. Other beta-blocker RCT: 1 (23) Cohort studies: 2 (77)	Improvement in IH	Low	In head-to-head comparisons, no significant differences in response between propranolol and atenolol in 2 studies; better response to nadolol vs. propranolol in one small study. Low SOE for no difference in response with propranolol, nadolol, or atenolol (systemic beta-blockers).
Oral propranolol vs. Intralesional bleomycin Cohort studies: 1 (20)	Improvement in IH	Insufficient	No difference between agents in one small study. Insufficient SOE due to single study with high limitations.
Topical timolol vs. Placebo or Observation Network meta-analysis RCT: 1 (41) Cohort studies: 2 (147)	Improvement in IH	Low	Timolol more effective than placebo or observation in three comparative studies. In network meta-analysis, the mean expected clearance rate for topical timolol was 62% (95% BCI: 39% to 83%) relative to 6% (95% BCI: 1% to 11%) for placebo or observation arms. Low SOE for effectiveness of timolol vs. placebo or observation based on medium study limitations and few studies.
Topical timolol vs. Topical imiquimod Cohort studies: 1 (38)	Improvement in IH	Insufficient	No significant differences in improvement in IH between groups. Insufficient SOE due to single study with high limitations.
Topical timolol vs. Timolol + PDL Cohort studies: 1 (102)	Improvement in IH	Insufficient	Timolol+PDL more effective than timolol alone (p=0.02) in one small study. Insufficient SOE due to single study with high limitations.
Topical timolol vs. PDL + Nd:YAG laserRCT: 1 (60)	Improvement in IH	Insufficient	Greater response to timolol among superficial IH and greater response to laser among mixed IH (p=NR). Insufficient SOE due to single study with high limitations.

Table C. Summary of evidence in studies addressing effectiveness of pharmacologic interventions (continued)

Intervention Type/ Number of Studies (Total N Participants)	Key Outcome(s)	Strength of Evidence (SOE) Grade	Findings
Oral propranolol RCT: 3 (515) Cohort studies: 5 (277) Case series: 16 (1274)	Significant and minor harms (significant: hypotension, bradycardia, bronchospasm, hypoglycemia; minor: cold extremities, diarrhea, sleep changes)	Moderate	Rates of clinically important harms ranged from 0 to 100% across studies and from 1% to 50% for minor harms. Moderate SOE for association of propranolol with these harms based on high study limitations.
Topical timolol RCT: 1 (41) Cohort studies: 4 (287) Case series: 1 (25)	Lack of harms	Low	No harms observed with timolol in 5 comparative studies and 1 case series. Shortness of breath and insomnia observed in 1 of 30 children in one comparative study. Low SOE for lack of association of timolol with harms based on few studies.
Oral nadolol Cohort studies: 1 (19)	Significant and minor harms (significant: hypotension, bradycardia, bronchospasm, hypoglycemia; minor: cold extremities, diarrhea, sleep changes)	Insufficient	Harms reported in 20% to 50% of children. Insufficient SOE due to single, small study with high limitations.
Oral atenolol RCT: 1 (23) Cohort studies: 1 (58)	Significant and minor harms (significant: hypotension; minor: cold extremities, diarrhea, sleep changes)	Insufficient	Harms reported ranged from 3% to 27% in 2 small studies Insufficient SOE due to high study limitations and few studies.

Abbreviations: BCI = Bayesian credible interval; IH = infantile hemangioma; PDL= pulse dye laser; RCT = randomized controlled trial; SOE = strength of evidence

Table D. Summary of evidence in studies addressing effectiveness of surgical interventions

Intervention Type/Number of Studies (Total N Participants)	Key Outcome(s)	Strength of Evidence (SOE) Grade	Findings
Lasers			
Longer pulse PDL vs other laser types and protocols RCT: 1 (52) Cohort studies: 2 (212)	Improvement in IH	Low	Resolution outcomes similar between laser types. Low SOE for no difference in effects on size reduction between longer pulse PDL and various other lasers given few studies, medium limitations, and inconsistent and imprecise findings.
PDL vs. Observation RCT: 2 (143)	Improvement in IH	Low	No significant difference in measured volume or proportion of clearance between groups; greater observer-ratings of improvement for PDL arm in one study. Low SOE for effectiveness of PDL vs. observation in reducing lesion size.
PDL vs. Observation RCT: 2 (143)	Quality of life	Low	No significant differences in parent ratings of QoL in one study; more parents of children in PDL arm in another considered appearance improved than in observation arm. Low SOE for no difference between PDL treatment and observation in reducing lesion size due to lack of precision, few studies..
Nd:YAG with extended cooling vs. Nd:YAG with standard cooling Cohort studies:1 (290)	Improvement in IH	Insufficient	Improved resolution with extended cooling protocol vs. traditional in single study with medium limitations. Insufficient SOE given single study with medium limitations.
Nd:YAG vs. CO2 laser vs. Tracheostomy Cohort studies: 1 (46)	Speech	Insufficient	75% of children with tracheostomy had delayed speech vs. 0 with no tracheostomy in the laser treatment era. Insufficient SOE given small, single study with high limitations.
PDL RCT: 2 (173) Cohort studies: 2 (73) Case series: 5 (1017)	Pigmentation changes	Moderate	Hypo- or hyper-pigmentation consistently reported, with hypopigmentation reported more frequently. Moderate SOE for association of PDL with skin pigmentation complications based on relatively few participants in studies.
PDL RCT: 1 (121)	Bleeding	Low	No significant difference in bleeding between short pulse PDL and observation groups. Low SOE for association of bleeding with PDL based on one study with low limitations, unknown consistency, and imprecision.

Table D. Summary of evidence in studies addressing effectiveness of surgical interventions (continued)

Intervention Type/Number of Studies (Total N Participants)	Key Outcome(s)	Strength of Evidence (SOE) Grade	Findings
PDL RCT: 1 (121)	Pain	Insufficient	13% of parents reported pain for their children after PDL. Insufficient SOE for pain following PDL given low numbers of outcome. Pain is also difficult to assess in infant population.
PDL Cohort studies: 1 (50) Case series: 3 (769)	Scarring	Insufficient	1/25 children receiving PDL in one study and 7/769 children in case series had scarring. Insufficient SOE due to few instances of the outcome reported in studies.
Nd: YAG Cohort studies: 1 (50)	Pigmentation changes	Insufficient	2/25 children receiving Nd:YAG in one study had scarring. Insufficient SOE due to few instances of the outcome reported in studies.
Nd: YAG Cohort studies: 3 (386) Case series: 3 (954)	Scarring	Low	Most studies reported scarring in ≤5% of children in 6 studies. Low SOE for association of scarring with Nd:YAG treatment due to few occurrences of the outcome reported.
Nd: YAG Case series: 2 (794)	Bleeding	Insufficient	Bleeding noted in 13/794 children in 2 studies. Insufficient SOE due to few instances of the outcome reported in studies.
Surgical			
Cryotherapy vs. Observation Comparative study: 1 (13)	Improvement in IH	Insufficient	76% of IH in treated arm vs. 12% in untreated resolved without scarring. Insufficient SOE given single, small study with high limitations.
Cryotherapy vs. Observation Comparative study: 1 (13)	Scarring	Insufficient	Scarring in 4 of 17 IH treated with cryotherapy. Insufficient SOE due to single, small study with high limitations.
Photo-thermolysis with Intense Pulsed Light With or Without Sclerosis vs. Cryotherapy Cohort studies: 1 (250)	Improvement in IH	Insufficient	More children had ≥50% reduction in IH size in the combined therapy arm than in other arms (p=NR). Insufficient SOE given single study with high limitations.

Table D. Summary of evidence in studies addressing effectiveness of surgical interventions (continued)

Intervention Type/Number of Studies (Total N Participants)	Key Outcome(s)	Strength of Evidence (SOE) Grade	Findings
Excision or resection Case series: 2 (142)	Scarring	Insufficient	Scarring in 11/192 children. Insufficient SOE due to few instances of the outcome reported in studies.
Excision or resection Case series: 7 (483)	Wound dehiscence	Insufficient	Dehiscences in 20/483 children. Insufficient SOE due to few instances of the outcome reported in studies with high limitations.

Abbreviations: BCI = Bayesian credible interval; IH = infantile hemangioma; Nd:YAG = neodymium- yttrium aluminum garnet; PDL= pulse dye laser; QoL = quality of life; RCT = randomized controlled trial; SOE = strength of evidence

Applicability

We set inclusion criteria intended to identify studies with applicability to children with IH between the ages of 0 and 18 years. Studies differed in terms of study population and outcome measures. Most studies included children with IH in multiple anatomic locations and did not report effectiveness by lesion site or type. Most studies were non-comparative, and lack of direct comparisons of treatment options and few studies addressing the same interventions and comparators further hinder our ability to understand what findings will best extrapolate to children at specific ages, with specific lesion types, or in specific anatomic locations. Further, most comparative studies were conducted in larger medical centers or referral centers, which is in line with typical treatment as most children with IH are referred to specialists from general practitioners.

Overall the available data on the effectiveness and harms of beta-blockers and corticosteroids are largely applicable to the general population of children with IH. Most studies included a majority of females, in line with the female predominance of IH, and ages in comparative studies generally ranged from 1 month to 9 years. One cohort study included individuals between 1 month and 43 years of age, with a mean age of 2 years and 11 months.

Few studies addressed imaging modalities, and those that did evaluated modalities to assess hepatic or intraspinal IH. Studies compared ultrasound, magnetic resonance imaging, computed tomography, and angiography. Imaging was sometimes not conducted at the same time, which limits comparability, and potentially the applicability of findings. Studies were also completed prior to 2010, so imaging techniques and practices may have changed.

Studies addressing steroids compared various routes of steroid administration (oral, topical, and intralesional) and various agents (methylprednisolone, triamcinolone, mometasone furoate) in children with ages ranging from less than 1 to 72 months. Studies likely included children with IH in the proliferative and involution phase, which may limit applicability to younger or older children. One comparative study was conducted in Canada and the others in Turkey, Pakistan, and India. Applicability may be limited given differences in the systems of care in lower resource countries. Comparative studies were also published between 2001 and 2010 and may not fully represent evolutions in standards of care.

Studies of beta-blockers typically included infants of both sexes ages 1 to 12 months of age (range: 1 month-9 years) with superficial, deep, and mixed lesions primarily involving the head and neck and occurring as focal or segmental lesions. Studies of topical or ophthalmic timolol typically included children with superficial lesions, though two of six comparative studies included children with superficial and deep lesions. Children were treated with a variety of beta-blockers including propranolol at various doses and administrations (oral, intralesional, or topical), timolol (topical or ophthalmic), atenolol (oral), or nadolol (oral), most commonly for up to 6 months duration. These agents and dosage forms are typically easily available in the United States and not universally available. Dosage amounts ranged from 1 to 4 mg/kg/day. Doses over 2 mg/kg/day are not typically administered and may limit applicability of findings of two studies of propranolol.

Surgical studies, conducted in the United States, the United Kingdom, the Netherlands, Germany, Greece, Japan and Singapore, included infants of both sexes with a preponderance of females (age range: 1 week to 43 years of age) with superficial and cutaneous infantile hemangiomas in varied locations. One study reported laser use for subglottic IH and one evaluated photothermolysis with intense pulsed light and cryosurgery in children of maxillary IH. Most comparative studies evaluated laser treatments including short-pulse and longer pulse PDL, Nd:YAG, and argon. Two studies evaluated cryotherapy, one of which compared it to photothermolysis with intense pulsed light with or without concomitant sclerosis. Applicability of many of these studies is limited by historical changes in care and technology.

Newer lasers and adjunctive features such as dynamic cooling have resulted in older lasers being out of date, thus limiting the applicability of studies conducted with those models. Most laser studies evaluated lasers as first-line treatment, which is currently less common in practice since the advent of beta-blocker treatment in countries, like the United States, where such treatments are readily available, as beta-blockers have generally superseded other treatments as first-line management of IH. Additionally, most comparative literature evaluated PDL, which is typically used only for the treatment of superficial lesions.

Limitations of the Evidence Base

The evidence base for IH treatment is limited by a small number of comparative studies including a limited number of participants. While cohort studies compared at least two different interventions, few presented truly comparative data. A number of studies reported only absolute differences in resolution or other outcomes, with no statistical comparison, in part likely due to their small sample sizes. Similarly, few studies reported baseline characteristics of the lesion, so understanding the magnitude of change reported is challenging. Most studies included children with problematic IH, so change was likely substantial, and parents and children may value any lessening of lesion size or change in color or texture.

A growing number of studies address beta-blockers, but current studies are limited by a general lack of long-term followup and analyses to explore differences in response among subgroups. Studies may also have used compounded forms of beta-blockers, which may add to the complexity of interpreting dosage amounts. Few comparative studies addressed steroids, and indications for steroid treatment compared with beta-blockers are unclear. Few comparative studies addressed surgical approaches besides laser modalities, and those addressing lasers used different interventions and comparators, limiting comparisons across studies. Technological advances have also changed the indications for treatment, and a historical trend towards treating smaller, less severe lesions, similarly make analyses difficult because of changing indications for and expectations of treatment.

Studies are also limited by the use of multiple and variable outcome measures to assess resolution of lesions. As no objective lab value or other measures exist to determine size changes, investigators have developed multiple techniques, and studies did not always report scales or other approaches clearly. The variety of scales (e.g., percentage change, mean change, visual analog scale, hemangioma activity score) make combining outcomes challenging. Similarly, studies typically included multiple lesion types in multiple locations, which complicates determining potential differences in response , and treatment approaches varied across studies (e.g., doses and dosage forms, level of patient monitoring, timing of treatment and followup).

The most important deficiency in the reported outcomes across studies is the tendency for the reporting of discretized outcomes, when the underlying outcome is a continuous variable. Specifically, though outcomes are likely recorded as a continuous measure (i.e., the proportion of an existing lesion that is cleared or reduced in size following treatment), authors often chose an arbitrary cutoff proportion (or a small number of bins) and reported only the numbers in each of the resulting categories. This results in an immediate and unrecoverable loss in power for any quantitative meta-analyses. Researchers should be encouraged to report outcome variables as they were recorded, without transforming them in such a way that information is lost. In addition, methods for measurement of outcomes such as rebound growth are not clearly reported; thus, our understanding of the magnitude of regrowth is limited.

Implications for Clinical and Policy Decisionmaking

This review provides evidence for use in clinical care of children who present with IH. It particularly points to moderate benefits with steroid treatment and greater improvements with beta-blockers, with propranolol being the most commonly studied. When a decision to treat is made, our review provides qualitative and quantitative evidence that beta-blockers are associated with substantial

improvement in IH size/volume (mean expected clearance rate of 95% for oral propranolol [95% BCI: 88% to 99%] and 62% [95% BCI: 39% to 83%] for topical timolol compared with 6% for observation/placebo arms [95% BCI: 1% to 11%]).

Steroids were associated with mean expected clearance rates of 43 percent for oral steroids (95% BCI: 21% to 66%) and 58 percent (95% BCI: 22% to 99%) for intralesional triamcinolone in our network meta-analysis, but side effects are significant, and clinicians and families will need to weigh the benefits and harms.

It is important for clinicians to know that the literature summarized here primarily examines children with problematic or complicated IH and thus may not apply to all patients. In one large trial evaluating active treatment with propranolol for children without problematic IH, propranolol was associated with complete resolution or near complete resolution in 60 percent of cases (vs. 4% in placebo arm). In addition, studies typically reported outcomes only in the short term (<12 months follow-up); thus, our understanding of the long-term effects of these medications is lacking. Further, though the literature demonstrates a strong shift towards beta-blocker therapy, uncertainty still remains about the most effective agent, dosage, and duration of treatment, and the need for pre-treatment evaluation and monitoring while on beta-blockers.

The literature identified to answer contextual questions (discussed fully in the main report) describes a broader range of indications for referral of patients with IH and suggests that indications for referral include large size; segmental type; risk for complications including bleeding, ulceration, and pain; involvement of critical structures; and risk factors for occult lesions (numerous cutaneous lesions, beard distribution). Further, the potential for psychosocial concerns would support referral for patients with uncomplicated lesions in highly visible areas on a case-by-case basis.

Limited research is available to guide decision-making about the use of laser modalities as the initial intervention. Historically, lasers provided a fair benefit in primary management of IH, which was comparable in many cases series to steroid treatment, and generally was superior to observation. The advent of propranolol has largely relegated laser treatment to secondary management. There is little comparative data between lasers and beta-blockers, however the success rates for complete or near complete resolution in historical laser studies are notably lower than those in more recent propranolol studies. Under current treatment paradigms, PDL with epidermal cooling is most often used for residual cutaneous changes after the completion of the proliferative growth phase and with incomplete resolution after pharmacologic management, while Nd:YAG laser is most often used intralesionally for medically refractory lesions. A variety of other lasers are used for intralesional treatment or resection, though no conclusions can be drawn regarding the superiority of any of these modalities over any other.

Given the lack of long-term data on harms of interventions, clinicians and families must balance the potential of both short- and long-term harms with the benefits of potential resolution or size reduction of lesions.

Research Gaps

While a growing number of comparative studies address treatments for IH, a number of research gaps exist. These gaps include a lack of information on:

- **Indications, optimal timing, and optimal modalities for imaging and diagnostic approaches**. Few studies in the literature we reviewed reported imaging or diagnostic techniques, and data on optimal approaches for each are lacking in the current research base. In general, imaging is infrequently used to differentiate accurately an IH from other vascular lesions. When a diagnosis is in question, a tissue biopsy is the most accurate method to determine the diagnosis. Future studies should use imaging modalities at the same point in the IH course to allow direct comparison. Studies should also report adverse effects of imaging, which are not addressed in the literature meeting criteria for this review.
- **Indications for treatment and treatment referral**. While it is likely that non-placebo-controlled studies reviewed here included mostly children with problematic IH (e.g., lesions that are vision-threatening or disfiguring, ulcerated lesions, airway/life-threatening lesions), studies did not always clearly report indications for treatment or referral for treatment. Children may be referred for life-, functional-, or vision-threatening reasons, but in the beta-blocker era, potential disfigurement is likely a cause for referral.
- **Appropriate dosing for propranolol and timing of treatment**. The largest RCT to date[28] used doses of either 1 mg/kg or 3 mg/kg, but other studies typically used doses of 2-2.5 mg/kg, and ages of children and number, severity, and type of lesions varied among study populations. Existing studies do not provide data to determine optimal dosing. Similarly, few

studies reported on resolution outcomes by phase (i.e., proliferative, involution). Studies likely included mostly children in the proliferative phase, but the effectiveness of propranolol during the involution phase is not clear. Similarly, because proliferation may occur up to and after 12 months of age, the effectiveness of starting beta-blockers in older children is not clear.

- **Optimal duration of beta-blocker use**. Duration of propranolol treatment ranged from 3 to 13 months in comparative studies, but the optimal duration of treatment is not clear. Studies generally treated children for 6 months, potentially so that effects observed were likely drug-related and not the result of natural involution. However, current studies have not addressed the question of optimal timing to achieve maximal benefit.
- **Long-term outcomes and harms of beta-blockers**. While harms reported in studies of beta-blockers were typically not severe, only one comparative study[29] had greater than 6 months followup after the end of treatment. Longer term effects on cardiovascular and metabolic parameters known to be affected by beta-blocker use as well as effects on cognition, memory, and the central nervous system are not well-understood in the population of very young children receiving beta-blockers for IH.[30]
- **Treatment choice for specific lesion types and locations**. Characteristics, such as lesion size, location, and persistence, as well as modifiers such as patient age, functional impact, and IH subtype influence whether children are treated with pharmacologic agents or surgically. Lesion characteristics also influence the choice of specific pharmacologic agents. Most studies included multiple lesion types and in multiple locations, and few included specific modifier analyses or reported outcomes by lesion characteristics. Research to improve understanding of which lesions are likely to respond best to specific agents is critical, especially as understanding of the effectiveness of beta-blockers in the involution phase is limited. Optimal treatment in the proliferative phase may be key to maximal resolution of IH.
- **Assessment of methods for assessing rebound growth**. A number of studies reported regrowth of lesions but typically did not indicate what constituted rebound growth. Greater clarity in reporting this outcome would help to clarify our understanding of effectiveness.
- **Characteristics that may influence response to beta-blockers**. Studies of beta-blockers were typically not powered to provide information on subgroups, but a percentage of children did not respond or responded minimally to propranolol. In 10 comparative studies of beta-blockers reporting these data,[15, 29, 31-39] 20 percent of children (n=63/314) had a limited or no response to the agent. We lack data to assess whether improvement in lesions or promotion of involution is affected by child age or number, severity, type, or anatomic location of lesions. Similarly, understanding the mechanisms of growth of IH will promote our understanding of response to treatments and treatment safety.
- **Use of beta-blockers other than propranolol**. Small cohort studies of oral atenolol and nadolol and topical or ophthalmic timolol showed positive effects on IH resolution with few side effects. Additional RCTs of these agents, with clear reporting of lesion parameters and child characteristics, would increase our understanding of their effectiveness and comparative effectiveness versus propranolol.
- **Treatments for hepatic IH**. Few treatment studies explicitly reported if children had hepatic IH. Most studies included children with IH in multiple locations, so children could have had hepatic IH as well; however, the applicability of findings to children with visceral IH is not clear.
- **Use of steroids and laser treatments in the beta-blocker era**. Clinical practice in the United States is moving toward use of a beta-blocker as the first-line treatment for IH;[40] however, a number of recent studies report use of steroids and laser treatments in younger children with lesions in the proliferative stage. Given the side effect profile of steroids, understanding of whether or when to use such agents in the absence of life-threatening lesions or contraindications to beta-blockers is needed. Current literature does not provide sufficient data to address these questions.
- **Interventions to follow beta-blockers or corticosteroids if such treatments fail**. We did not identify any studies that clearly reported data on this question. While most children receiving beta-blockers in the studies reviewed here responded to the medication, some had no or minimal response.
- **Standardization of scoring tools to assess change in IH**. IH outcomes are necessarily assessed using subjective measures, and investigators typically reported grading scales used to assess change

in IH size or appearance. Few studies, however, commented on interrater reliability of instruments. Research to improve standardization among tools and the development of uniform scoring systems and measurements would improve our ability to combine outcomes across studies.

- **Standardization of nomenclature**. Data extraction and comparisons in the review were limited by inconsistent naming conventions. Agreement and adherence to a standard classification of lesions would improve the ability of researchers to focus on individual lesion types and determine optimal treatment regimens for specific lesions.

Conclusions

Corticosteroids demonstrate some effectiveness at reducing IH size/volume, but may be associated with significant side effects. Propranolol is effective at reducing the size of IH, with high strength of evidence for effects on reducing lesion size, and compared with placebo, observation, and other treatment methods including steroids in most, but not all, studies. In a network meta-analysis, the largest mean estimate of expected clearance was for oral propranolol (95%, 95% BCI: 88% to 99%), followed by timolol (62%, 95% BCI: 39% to 83%) and triamcinolone (58%, 95% BCI: 22% to 93%). The mean rate was 43 percent for oral steroids (95% BCI: 21% to 66%). With fairly wide confidence bounds and limited data in some areas, the relative differences among these estimates are of greater importance than the absolute effects. The estimates provide a relative ranking of anticipated rates of lesion clearance among treatment options. Families and clinicians making treatment decisions should also factor in elements such as lesion size, location, type, and number, which may affect choice of treatment modality, as well as patient/family preferences. Evidence pointed to substantial side effects for corticosteroids; harms were also noted with beta-blockers, but overall, these were well tolerated in the short term. Few studies have assessed potential long-term harms associated with beta-blocker use in infants and children. Laser studies generally found PDL more effective than other types of laser, but effects remain unclear as studies are heterogeneous and the role of laser vis-a-vis beta-blockers is not clearly described in the literature. Data are inadequate to address the role of imaging in guiding treatment.

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Full Report

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