Draft Comparative Effectiveness Review

Number XX

Diagnosis and Management of Infantile Hemangioma

Prepared for:
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Contract No.

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AHRQ Publication No. xx
<Month Year>

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Suggested citation:

Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of systematic reviews to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. These reviews provide comprehensive, science-based information on common, costly medical conditions, and new health care technologies and strategies.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews can help clarify whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about AHRQ EPC systematic reviews, see www.effectivehealthcare.ahrq.gov/reference/purpose.cfm.

AHRQ expects that these systematic reviews will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. Transparency and stakeholder input are essential to the Effective Health Care Program. Please visit the Web site (www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an email list to learn about new program products and opportunities for input.

We welcome comments on this systematic review. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by email to epc@ahrq.hhs.gov.

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Acknowledgments

The authors gratefully acknowledge the following individuals for their contributions to this project: [to be added]

Key Informants

In designing the study questions, the EPC consulted several Key Informants who represent the end-users of research. The EPC sought the Key Informant input on the priority areas for research and synthesis. Key Informants are not involved in the analysis of the evidence or the writing of the report. Therefore, in the end, study questions, design, methodological approaches, and/or conclusions do not necessarily represent the views of individual Key Informants.

Key Informants must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their role as end-users, individuals with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any conflicts of interest.

The list of Key Informants who participated in developing this report follows:

[to be added]

Technical Expert Panel

In designing the study questions and methodology at the outset of this report, the EPC consulted several technical and content experts. Broad expertise and perspectives were sought. Divergent and conflicted opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore, in the end, study questions, design, methodologic approaches, and/or conclusions do not necessarily represent the views of individual technical and content experts.

Technical Experts must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

The list of Technical Experts who participated in developing this report follows:

[to be added]

Peer Reviewers

Prior to publication of the final evidence report, EPCs sought input from independent Peer Reviewers without financial conflicts of interest. However, the conclusions and synthesis of the scientific literature presented in this report do not necessarily represent the views of individual reviewers.

Peer Reviewers must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential nonfinancial conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential nonfinancial conflicts of interest identified.

The list of Peer Reviewers follows:

[to be added]

Diagnosis and Management of Infantile Hemangioma

Objectives. To systematically review evidence addressing the diagnosis and management of infantile hemangiomas (IH).

Data sources. We searched the MEDLINE®, Embase, and Cumulative Index to Nursing and Allied Health Literature (CINAHL®) databases for diagnostic and intervention studies published in English since 1982. We searched these databases without date restrictions for contextual information.

Review methods. We included comparative studies of imaging and pharmacologic and surgical interventions published in English from 1982 to October 2014. We also included case series addressing harms of interventions and case series and systematic and narrative reviews to address contextual questions. Two investigators independently screened studies against predetermined inclusion criteria and independently rated study quality. We extracted data into evidence and summary tables and summarized them qualitatively and quantitatively via network meta-analysis. We also assessed the strength of the evidence for key interventions and outcomes.

Results. We identified a total of 111 unique studies. Thirty-four studies addressed effectiveness outcomes (6 good, 18 fair, and 10 poor quality), and 108 studies reported harms of interventions (14 good, 2 fair, and 92 poor quality). Two small, poor quality 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. Studies of steroids assessed different agents, and children in treatment arms typically had improvement in lesion size. Harms of steroids were varied and frequently included Cushingoid facies, irritability/mood changes, and growth retardation. Beta-blockers typically demonstrated significantly greater effects on reducing lesion size or volume than did control or other active comparators. In meta-analysis, the largest mean estimate of expected clearance was for oral propranolol (95%; 95% Bayesian credible interval: 86% to 100%) relative to oral corticosteroids (29%) and control (2%). Harms most frequently reported with beta-blockers included hypotension, hypoglycemia, bradycardia, sleep disturbances, cold extremities, gastrointestinal symptoms, and bronchial irritation. Comparative studies of surgical interventions all addressed laser treatment, typically variations of pulse dye laser (PDL). Most studies reported a higher success rate with long pulse PDL compared to observation in managing the size of IH, although the magnitude of effect differed substantially. Harms associated with laser treatment included hypopigmentation and scarring. No studies evaluated second-line treatments following failure of beta-blockers or corticosteroids. 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; risk factors for occult lesions (numerous cutaneous lesions, beard distribution); and the potential for psychosocial concerns in some cases. Multiple case series reported associations between multiple cutaneous lesions and airway or hepatic IH and facial lesions in a beard distribution and airway IH.

Conclusions. Corticosteroids demonstrated moderate effectiveness at reducing IH size/volume (moderate strength of evidence [SOE] for improvement in IH with oral steroids compared with observation/placebo; low SOE for intralesional steroids vs. observation/placebo; moderate SOE

for association with clinically important harms). Propranolol had high SOE for effects on reducing lesion size compared with observation/placebo. Clearance of IH was greater in propranolol arms compared with placebo, observation, and other treatment methods including steroids in most, but not all, studies. Meta-analysis results indicated high mean rates of IH clearance with oral propranolol (95%) and moderate rates for steroids (29% to 53%; moderate SOE for effects of propranolol compared with steroids). Beta-blockers and steroids also may cause clinically important side effects (moderate SOE for association of propranolol with harms). No 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 (insufficient to low SOE for effects of laser types on IH clearance; moderate SOE for association of PDL with skin pigmentation changes; low SOE for association with pain). Data were inadequate to address the role of imaging in guiding treatment (insufficient SOE). Information from our contextual review describes a broad range of indications for referral of patients with IH and suggests support for a higher index of suspicion 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.

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Executive Summary

Introduction

Infantile hemangiomas (IH) are the most common tumors of childhood. IH are vascular tumors that, while benign, possess potential for local tissue destruction, infection, bleeding, and pain. 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,[1] with higher prevalence in females and Caucasians.[2 3] IH tend to go through growth, plateau, 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 months.[4] 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 cosmetic disfigurement and functional compromise.[5] Early assessment of the extent of the hemangioma, and early, appropriate treatment of IH may potentially mitigate these complications. Furthermore, some lesions are particularly aggressive or morbid and can cause severe pain, ulceration, and bleeding even in early stages.[6, 7] 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).[8-10]

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. 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.

Specific disease characteristics, such as lesion size, location, and persistence as well as modifiers such as patient age, functional impact, and hemangioma subtype may influence whether children are treated with pharmacologic agents or surgically. Most lesions can be treated with pharmacologic agents; however, lesions that possess immediate risk for morbidity or mortality, such as hemangiomas obstructing the airway, may require more immediate surgical intervention. Potential psychosocial impact may also help determine treatment. 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 cosmetic 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

Propranolol was approved by the U.S. Food and Drug Administration (FDA) for use in IH in March 2014.[11-13] Prior to this, corticosteroids were the drug of choice, and there is still disagreement about which medication represents the best choice for initial medical management. Additionally, there is no clear consensus as to when alternative or adjunctive medications such as chemotherapeutic drugs are appropriate after first-line treatment is unsuccessful.[14, 15]

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); therefore, universal treatment is unwarranted.

Scope and Key Questions

Scope of 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 provide a narrative review of relevant literature for contextual questions in the full report as few effectiveness studies address these questions, which are related to natural history of IH and markers for occult hemangiomas.

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 website. Questions were as follows:

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)?

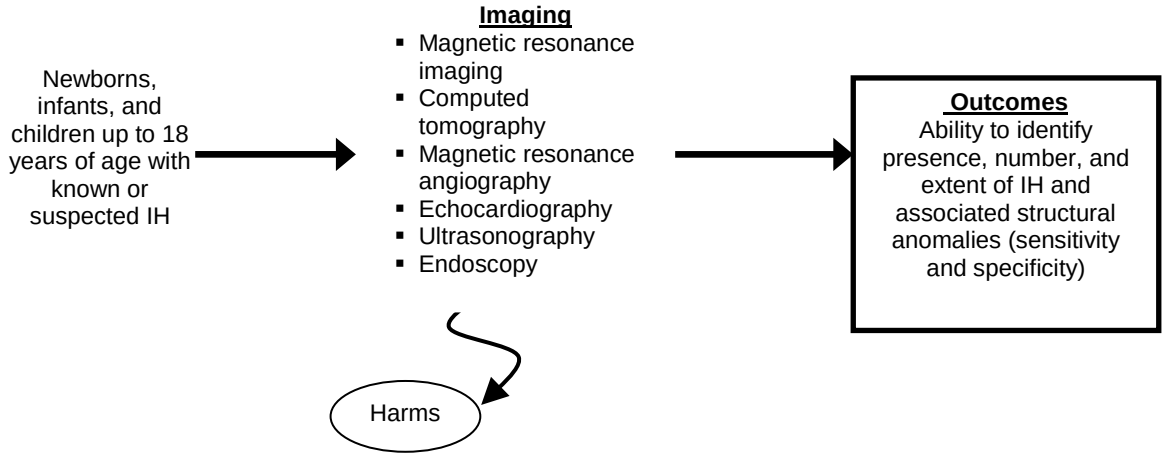
CQ1. What is known about the natural history of infantile hemangiomas, by hemangioma site and subtype? What are the adverse outcomes of untreated infantile hemangiomas? What characteristics of the hemangioma (e.g., subtype, size, location, number of lesions) indicate risk of significant medical complications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

Analytic Framework

The analytic frameworks illustrate the population, interventions, and outcomes that guided the literature search and synthesis of comparative studies. The frameworks depict the Key Questions 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

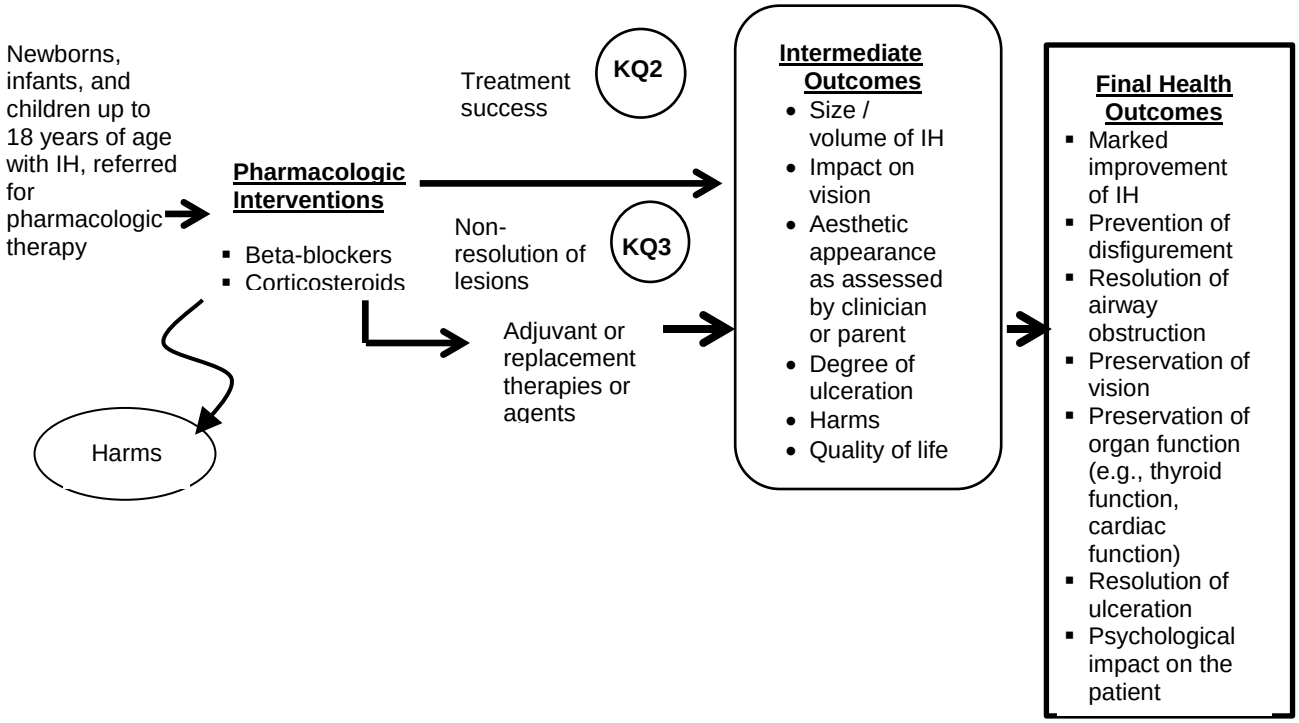
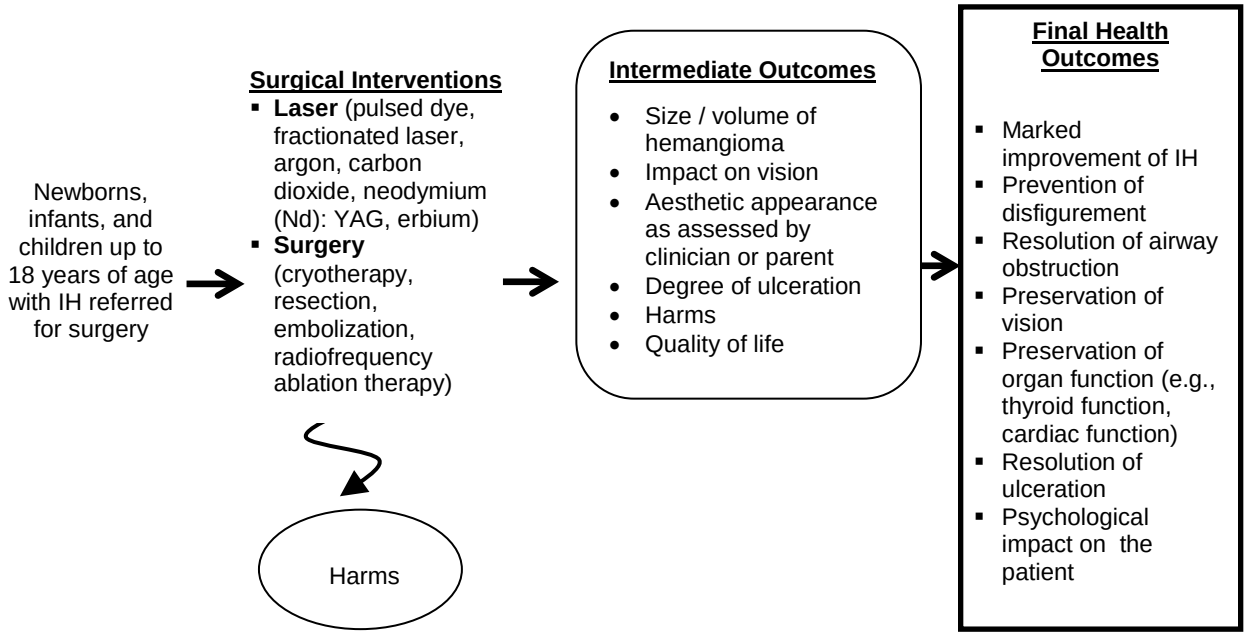


Figure C. Analytic framework for KQ4



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.[16] We searched the same databases without date restrictions to identify contextual information. Our last search was conducted in October 2014. 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	<u>Admissible designs</u> 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

Category	Criteria
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) • 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 Key Question 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 Key Question, with any disagreements adjudicated by a senior reviewer. Reviewers could flag studies that potentially addressed a Contextual Question identified in the screening process for Key Questions.

We also screened studies identified in our separate database searches for studies potentially addressing Contextual Questions. We did not conduct dual screening of studies identified in our searches for Contextual Questions. If one reviewer determined that a study could be eligible, we assessed its relevance to the Contextual Questions. 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 Key Questions are available in the Systematic Review Data Repository.

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

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: propranolol, triamcinolone, timolol, or oral steroid.

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 Key Questions: questions adapted from the RTI item bank to assess RCTs,[17] the Newcastle-Ottawa Quality Assessment Scale for cohort studies,[18] the QUADAS tool for diagnostic imaging studies,[19] and a tool adapted from questions outlined in the RTI item bank and the McMaster McHarms tool to assess reporting of harms.[20]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 body of 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.*[21] 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 strength of evidence for the Key Questions only.

Applicability

We assessed the applicability of findings reported in the included literature addressing Key Questions 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

Article Selection and Overview

We identified 3714 nonduplicative titles or abstracts with potential relevance, with 1117 proceeding to full text review. We included 111 unique studies (114 publications) in the review. Among these 111 studies, 34 comparative studies addressed the effectiveness and harms of therapies, and 77 case series addressed harms. The 111 unique studies included in the review comprise 12 randomized controlled trials (RCTs), five prospective and 15 retrospective cohort studies, two diagnostic accuracy studies (defined as studies that compared the accuracy of imaging modalities in identifying or characterizing IH), and 77 case series (used for harms data only). We considered six comparative studies to be good quality, 18 fair quality, and 10 poor quality. One-hundred and eight studies (comparative studies and case series) reported harms/adverse events data. We considered 14 of these as good quality for harms reporting, two as fair quality, and the remainder (n = 92) as poor quality for harms reporting.

Contextual Questions

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.

KQ1. Effectiveness and Harms of Imaging Modalities for IH

Two poor quality diagnostic accuracy studies addressed imaging modalities.[22, 23] 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% (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

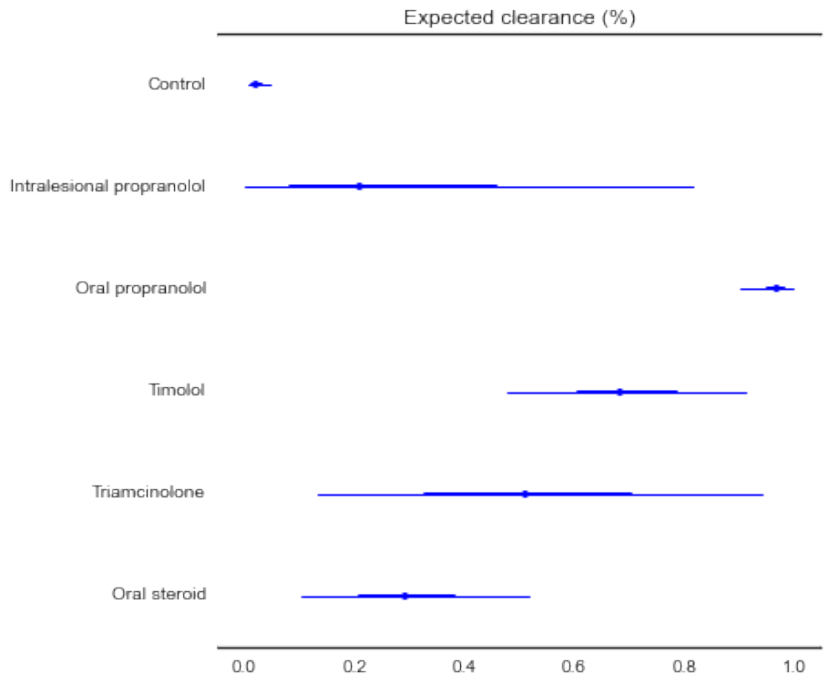
Summary of Meta-Analysis Results

We included 17 studies in a network meta-analysis. All studies addressed pharmacologic agents and included four RCTs and five cohort studies evaluating propranolol and placebo or observation or another active agent; one RCT and one cohort study comparing propranolol and other beta-blockers; three cohort studies and one RCT assessing timolol compared with placebo or observation or another agent; and one RCT and one cohort study evaluating different steroids. Studies included a total of 1144 children with IH.

In our network meta-analysis, propranolol had the highest clearance rate. As described in the qualitative results, there were substantially more studies of propranolol available for inclusion in the analysis. The expected efficacy of control arms was estimated to be 2 percent (95% BCI: 0% to 5%), 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: 86% to 100%), followed by timolol (64%, 95% BCI: 31% to 90%), and triamcinolone (53%, 95% BCI: 14% to 97%). Oral steroids had a rate of 29 percent (95% BCI: 9% to 50%).

The variation in treatment outcomes was high in beta-blocker studies. Thus, the potential for greater clearance was much higher in patients treated with 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).

Corticosteroids

We identified 18 studies (three RCTs, one cohort study, and 14 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 3155. 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 29 percent (95% Bayesian credible interval [BCI]: 9% to 50%) and intralesional triamcinolone had a rate of 53 percent (95% BCI: 14% to 97%) with wide confidence boundaries.

Overall, there is adequate evidence to support a moderate SOE for oral steroids to have a modest effect 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 one 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

Fifty seven studies (19 comparative studies and 38 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 2 percent (95% BCI: 0% to 5%) in placebo or observation arms, oral propranolol had a rate of 95 percent (95% BCI: 86% to 100%). 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 children in case series and no children in comparative studies).

Propranolol versus Observation or Placebo. We identified three studies (two good 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 three studies. In the largest RCT, which included 456 children without problematic IH receiving 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 findings and in individual studies, IH size reductions were greater in propranolol arms vs. control, thus we considered the SOE as high for greater effectiveness of propranolol compared with placebo or observation.

Propranolol versus Other Active Modalities. Eight studies (one RCT of good quality; six fair and one poor quality cohort studies) compared propranolol to another modality including steroids, pulse dye laser [PDL], bleomycin, or historical treatments in a total of 318 children. In head-to-head comparisons, studies of propranolol and steroids had conflicting findings.

Propranolol was more effective than steroids in two studies, while two others studies did not find effectiveness differed significantly between these treatments. In network meta-analysis, oral propranolol was associated with a mean estimate of expected clearance of IH of 95% (BCI: 86% to 100%) compared with lower rates for oral steroids (29% (95% BCI: 9% to 50%). One 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.

In head-to-head comparisons, propranolol was more effective than steroids in two studies; two other studies reported no significant difference between propranolol and steroids. In network meta-analysis, pulling data from multiple studies, propranolol was superior to oral steroids (95% clearance versus 29% clearance). These combined effects from individual studies and meta-analysis conferred moderate SOE for superiority of propranolol over steroids at achieving clearance.

Oral Propranolol vs. Other Beta-Blockers or Dosage Forms. Three small studies (n=145, one fair quality RCT; one fair and one poor quality cohort study) compared propranolol with nadolol or atenolol, and one fair quality cohort study evaluated oral, intralesional, and topical propranolol. Atenolol and nadolol demonstrated promising effects on lesion size (largely equivalent effectiveness of propranolol and atenolol and greater effectiveness 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 (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 vs. propranolol in one small study. We considered the SOE as low for an equivalent response with propranolol, nadolol, or atenolol (systemic beta-blockers).

Timolol vs. Placebo/Observation or Other Active Modality. Four studies addressed timolol (one good quality RCT and two fair and one poor quality cohort studies including 228 children). Timolol was significantly more effective than observation or placebo in three studies, and one study comparing imiquimod with timolol did not demonstrate that one intervention was more effective than the other. In our network meta-analysis, topical timolol had a mean expected clearance rate of 64 percent (95% BCI: 31% to 90%) compared with 2 percent (95% BCI: 0% to 5%) for placebo or observation. We considered SOE as low for the effectiveness of timolol compared with placebo or observation. No harms of timolol were observed in any study. We considered SOE to be low for lack of association of timolol with harms.

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

Nine comparative studies (three RCTs and six retrospective cohort studies including a total of 766 children) and 25 case series (n=2428) addressed surgical approaches. We considered one RCT as good, two RCTs and two cohort studies as fair, and four cohort studies as poor quality. Comparative studies were typically small (≤55 participants), though one RCT and two retrospective cohort studies included more than 120 children. Lasers studied varied across studies in type, pulse width, or cooling materials. Most studies assessed variations of PDL (n=7) and examined heterogeneous endpoints. All studies except one reported on treatment of cutaneous lesions, and comparators included observation or other laser modalities. Several studies used historical controls, based on now superseded treatment regimens. No other surgical methods were evaluated in comparative studies.

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. e. One reported no differences in level of reduction between traditional and long-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, long 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 long pulse PDL compared to observation in managing the size of IH, although the magnitude of effect differed substantially. CO_2 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.

SOE for outcomes after laser treatments ranged from insufficient to low for effectiveness outcomes. The evidence was limited by low sample size, and variations in the laser settings used including wavelength and cooling protocols. For Nd:YAG and CO_2 lasers, all studies were limited by sample size, and SOE was insufficient for 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 (Table 36).

Studies of Surgical Treatment

No comparative studies addressed surgical approaches. 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 Contextual Questions

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 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 Key Questions

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 with the exception of no significant differences in reducing lesion size in two studies comparing it to steroids. 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 Key Questions about interventions for children with IH ranged from insufficient to moderate when the comparisons are made with the individual studies qualitatively. A 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 (Table B).

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. 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 29 percent (95% BCI: 9% to 50%), and intralesional triamcinolone had a rate of 65 percent (95% BCI: 14% to 97%) 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, there is adequate evidence to support a moderate strength of evidence for oral steroids to have a modest effect 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.

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 2 percent (95% BCI: 0% to 5%) in placebo or observation arms and 29% for oral steroids, the mean estimated clearance rate for oral propranolol was much higher (95%) in our 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% (95% BCI: 86% to 100%) compared with a lower rate for oral steroids of 29% (95% BCI: 9% to 50%). 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 64 percent.

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 an equivalent response of 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.

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. 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 and interventions

Intervention Category	Intervention Type/Number of Studies (Total N Participants)	Key Outcome(s)	Strength of Evidence (SOE) Grade	Findings
Imaging	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 in a 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) in a single small study with high study limitations.
Steroids	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 29% compared with 2% for placebo/observation arms.
	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 53% compared with 2% 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: 9 (2944)	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.
Beta-Blockers	Propranolol vs. Placebo or Observation Network meta-analysis RCT: 2 (496) Cohort studies: 1 (45)	Improvement in IH	High	In network meta-analysis, the mean expected clearance rate for oral propranolol was 95% relative to 2% 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.

Intervention Category	Intervention Type/Number of Studies (Total N Participants)	Key Outcome(s)	Strength of Evidence (SOE) Grade	Findings
	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.
	Propranolol vs. Steroids Network meta-analysis RCT: 1 (19) Cohort studies: 3 (156)	Improvement in IH	Moderate	In head-to-head comparisons, propranolol more effective than steroids in 2 studies; 2 other studies reported no significant difference between propranolol and steroids. In network meta-analysis, pulling data from multiple studies, propranolol was superior to oral steroids (95% clearance versus 29% clearance). Combined effects from individual studies and meta-analysis confer moderate SOE for superiority of propranolol over steroids at achieving clearance.
	Propranolol vs. Other beta-blocker Network meta-analysis 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 equivalent response with propranolol, nadolol, or atenolol (systemic beta-blockers).
	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 64% relative to 2% for placebo or observation arms. Low SOE for effectiveness of timolol vs. placebo or observation based on the need for additional studies.
	Propranolol (topical, oral, intralesional) RCT: 4 (560) Cohort studies: 5 (277) Case series: 5	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.

Intervention Category	Intervention Type/Number of Studies (Total N Participants)	Key Outcome(s)	Strength of Evidence (SOE) Grade	Findings
	(657)			
	Timolol RCT: 1 (41) Cohort studies: 3 (185)	Lack of harms	Low	No harms observed in 4 small studies with medium limitations. Low SOE for lack of association of timolol with harms.
	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 in a single, small study with high limitations.
	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 3 small studies with high limitations.
Laser Treatments	Long-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 for difference in effects on size reduction between long-pulse PDL and other lasers.
	PDL vs. Observation RCT: 2 (143)	Improvement in IH	Low	No significant difference in measured volume or proportion of clearance between groups in either study when considering complete and near complete clearance; greater observer-ratings of cosmetic improvement for PDL arm in one study. Low for effectiveness of PDL in reducing lesion size vs. observation.
	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 cosmetic appearance improved than in observation arm. Low SOE for lack of difference in QoL with PDL compared with observation.
	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.

Intervention Category	Intervention Type/Number of Studies (Total N Participants)	Key Outcome(s)	Strength of Evidence (SOE) Grade	Findings
	Nd:YAG vs. CO_2 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 in small, single study with high limitations.
	PDL RCT: 2 (173) Cohort studies: 2 (73) Case series: 3 (317)	Pigmentation changes	Moderate	Hypo- or hyper-pigmentation consistently reported, with hypopigmentation reported more frequently. Moderate SOE for association of PDL with skin pigmentation complications.
	PDL RCT: 1 (121)	Bleeding	Low	No significant difference in bleeding between short pulse PDL and observation groups. Low SOE for association of bleeding and PDL
	PDL RCT: 1 (121)	Pain	Insufficient	13% of parents reported pain for their children after PDL; low numbers of outcome. Pain is also difficult to assess in infant population.
	PDL Cohort studies: 1 (50) Case series: 1 (69)	Scarring	Insufficient	1/25 children receiving PDL in one study and unstated number in another had scarring; very small numbers of the outcome reported.
	Nd: YAG Cohort studies: 1 (50)	Pigmentation changes	Insufficient	2/25 children receiving Nd:YAG in one study had scarring; very small numbers of the outcome reported.
	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.
	Nd: YAG Case series: 2 (794)	Bleeding	Insufficient	Bleeding noted in 13/794 children in 2 studies; small numbers of the outcome reported.

Abbreviations: CT = computed tomography; IH = infantile hemangioma; IV = intravenous; MRI = magnetic resonance imaging; Nd:YAG = neodymium-doped yttrium aluminum garnet; PDL= pulse dye laser; QoL = quality of life; RCT = randomized controlled trial

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 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 these 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. Children were treated with a variety of beta-blockers including propranolol at various doses and administrations (oral, intralesional, or topical), timolol (topical), 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.

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. All comparative studies evaluated laser treatments including short-pulse and long-pulse PDL, Nd:YAG, and argon. Applicability of many of these studies is limited by historical changes in care and technology. 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 where such treatments are readily available. Further, 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.

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 . Future studies should use imaging modalities at the same point in the IH course to allow direct comparison.
- **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 cosmetically displeasing, 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, cosmetic issues are likely a cause for referral.
- **Appropriate dosing for propranolol and timing of treatment.** The largest RCT to date[24] 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 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 are not well-understood in the population of very young children receiving beta-blockers for 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, 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.

- **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;[25] however, a number of recent studies report use of steroids and laser treatments in younger children with lesions in the proliferative stage. Given the significant side effect profile of steroids, understanding of whether or when to use such agents in the absence of life-threatening lesions is needed. Similarly, steroids may be best used in children in the involution stage to clear residual markings or in children with threatening airway lesions, but 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 would improve our ability to combine outcomes across studies.

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 lack of long-term followup and analyses to explore differences in response among subgroups. Few comparative studies addressed steroids, and indications for steroid treatment compared with beta-blockers are unclear. No 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, VAS, HAS) make combining outcomes challenging.

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 and 64% for topical timolol compared with 2% for observation/placebo arms).

Steroids were associated with mean expected clearance rates of 29 percent for oral steroids and 53 percent for intralesional triamcinolone in our 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 no 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.

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: 86% to 100%), followed by timolol (64%, 95% BCI: 31% to 90%) and triamcinolone (53%, 95% BCI: 14% to 97%). The mean rate was 29 percent for oral steroids. 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. No 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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Introduction

Background

Infantile hemangiomas (IH) are the most common tumors of childhood. IH are vascular tumors that, while benign, possess potential for local tissue damage, infection, bleeding, functional impact, and pain. Due to historical inconsistencies in naming conventions, it is difficult to know the true prevalence of IH, but it is estimated that they affect about 4 to 5 percent of children,[1] with higher prevalence in females and Caucasians.[2, 3] The most common locations are the head, neck, and trunk, but they can occur almost anywhere throughout the body, including the extremities, the spine, and visceral organs.[4-6] IH also can be associated with a constellation of congenital anomalies such as PHACES (posterior fossa malformations, hemangiomas, arterial anomalies, cardiac defects, eye abnormalities, sternal cleft and supraumbilical raphe) PELVIS (perineal hemangioma, external genitalia malformations, lipomyelomeningocele, vesicorenal abnormalities, imperforate anus, and skin tag) and LUMBAR (lower-body hemangioma and other cutaneous defects, urogenital anomalies, ulceration, myelopathy, bony deformities, anorectal malformations, arterial anomalies, and renal anomalies) syndromes.

IH tend to go through growth, plateau, and involution phases, although the complete natural history of IH 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 3 months.[7] With 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 cosmetic disfigurement and functional compromise.[8] Early assessment of the extent of the hemangioma, and early, appropriate treatment of IH may potentially mitigate these complications. Furthermore, some lesions are particularly aggressive or morbid and can cause severe pain, ulceration, and bleeding even in early stages.[9, 10] 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 IH such as those associated with syndromes like PHACES, LUMBAR, or PELVIS, 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).[4, 6, 11]

Diagnosis and Treatment Decisions

Evaluation through the use of various diagnostic imaging modalities has been generally been reserved for deep lesions to help understand their extent. 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 many imaging studies in infants often require general anesthesia.

Specific disease characteristics, such as lesion size, location, and persistence as well as modifiers such as patient age, functional impact, and hemangioma subtype influence whether children are treated with pharmacologic agents or surgically. Many lesions can be treated with

pharmacologic agents; however, lesions that possess immediate risk for morbidity or mortality, such as IH obstructing the airway, may require more immediate surgical intervention. 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, such as ocular IH disrupting the development of neural pathways during infancy. Further, some lesions, such as nasal tip IH, may cause permanent structural changes to adjacent structures. This may result in severe functional and cosmetic sequelae, even with complete resolution of the IH itself. 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

Propranolol was approved by the U.S. Food and Drug Administration (FDA) for use in IH in March 2014.[12-14] Prior to this, corticosteroids were the drug of choice, and there is still some disagreement about which medication represents the best choice for initial medical management.[15] Additionally, there is no clear consensus as to when alternative or adjunctive medications such as chemotherapeutic drugs are appropriate after first-line treatment is unsuccessful.[16, 17]

Surgical interventions for IH can be used for primary management of high risk lesions and include 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); therefore, universal treatment is not recommended.[18]

Scope and Key Questions

Scope of 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 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.

Key Questions

Key Questions (KQs) and Contextual Questions (CQs) were developed in consultation with Key Informants and the Task Order Officer and were posted for review to the AHRQ Effective Health Care website. 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?

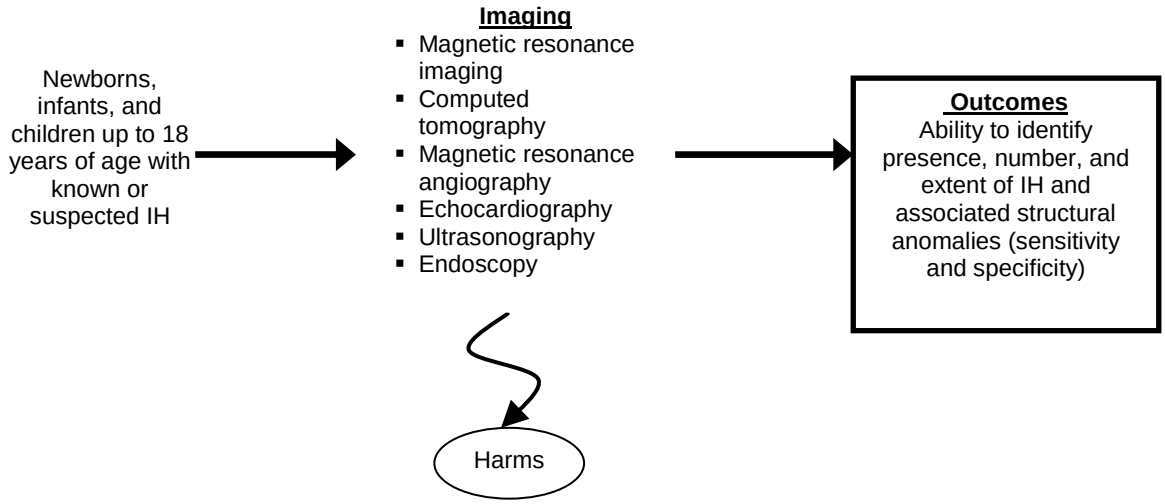
KQ3. Among newborns, infants, and children up to 18 years of age with infantile hemangiomas for whom treatment with corticosteroids or beta-blockers is unsuccessful what is the comparative effectiveness of second line therapies including immunomodulators and angiotensin-converting enzyme inhibitors?

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

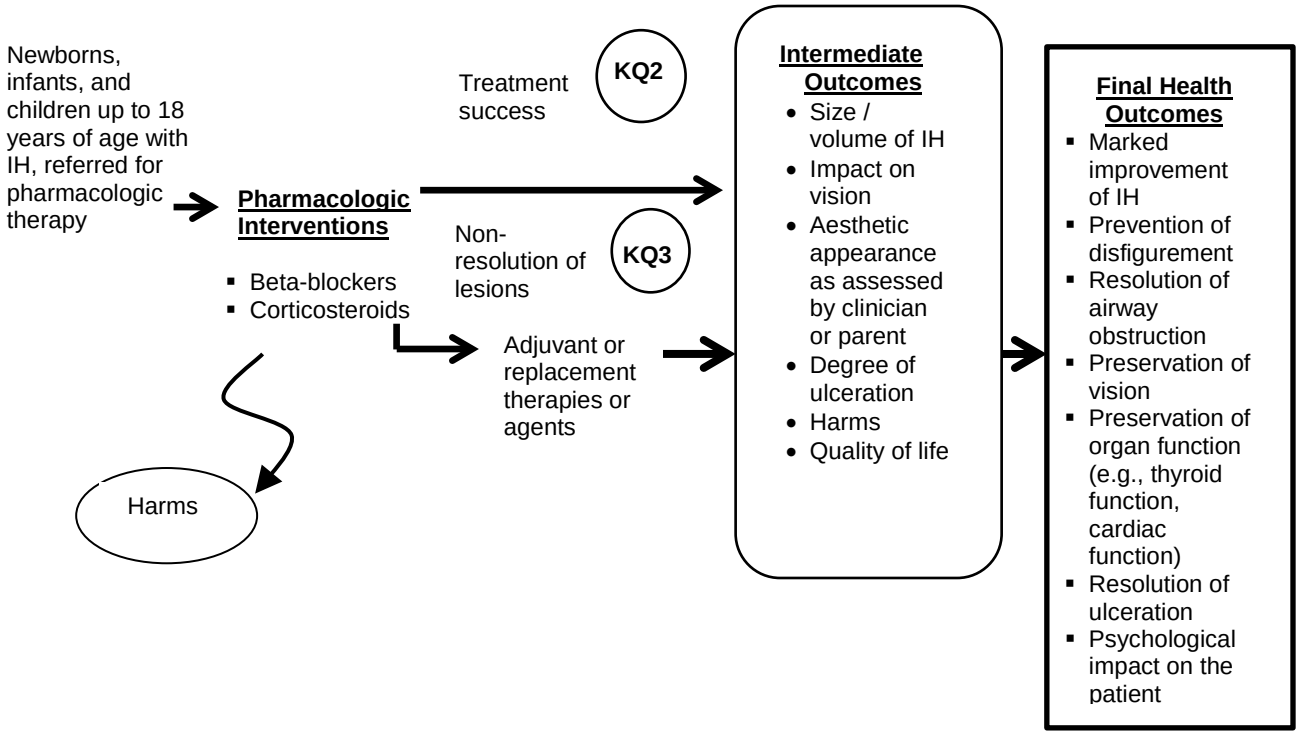
The analytic frameworks illustrate the population, interventions, and outcomes that guided the literature search and synthesis. The frameworks depict the key questions within the context of the population, intervention, comparator, outcomes, timing, and setting (PICOTS) parameters described in the review. 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 IH 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 the intervention is received.

Figure 1. Analytic framework for KQ1



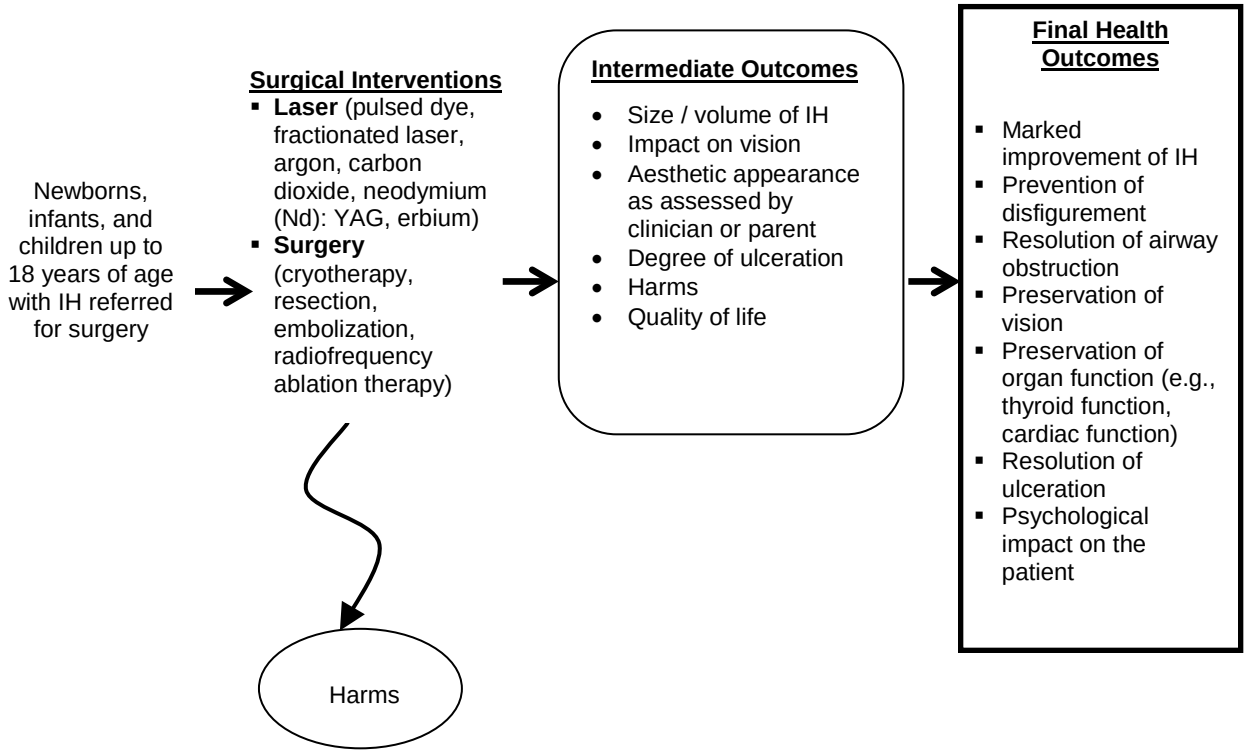
Abbreviations: IH = infantile hemangioma; KQ = key question

Figure 2. Analytic framework for KQ2 and KQ3



Abbreviations: IH = infantile hemangioma; KQ = key question

Figure 3. Analytic framework for KQ4



Abbreviations: IH = infantile hemangioma; KQ = key question; Nd:YAG = neodymium yttrium aluminum garnet

Organization of This Report

The Methods section describes the review processes including search strategy, inclusion and exclusion criteria, approach to review of abstracts and full publications, methods for extraction of data, and compiling evidence. We also describe our approach to grading the quality of the literature and describing the strength of the body of evidence.

The Results section presents the findings of the literature search and the review of the evidence by key question, synthesizing the findings across strategies. We present findings by intervention and outcome area where possible under each key question and focus on comparative studies of higher quality. Summary tables for each KQ outline key outcomes.

The Discussion section of the report discusses the results and expands on methodologic considerations relevant to each KQ. We also outline the current state of the literature and challenges for future research in the field.

The report includes a number of appendices to provide further detail on our methods and the studies assessed. The appendices are as follows:

- Appendix A: Search Strategies
- Appendix B: Screening and Quality Assessment Forms
- Appendix C: Excluded Studies
- Appendix D: Methods for Meta-Analysis

- Appendix E: Study Design Classification Algorithm
- Appendix F: Quality/Risk of Bias Scoring
- Appendix G: Applicability Tables
- Appendix H: Harms Reported in Package Insert Data and Other Sources

We also provide a list of abbreviations and acronyms at the end of the report.

Uses of This Evidence Report

We anticipate this report will be of primary value to organizations that develop guidelines for managing IH and to clinicians who provide care for children with IH and for families making treatment decisions. Interested organizations would include the American Academy of Pediatrics, the American Academy of Otolaryngology-Head and Neck Surgery, the Society for Pediatric Dermatology, the American society of Pediatric Otolaryngology, the Vascular Birthmarks Foundation, the Society of Pediatric Nurses, the American Society for Pediatric Hematology and Oncology, the National Association of Nurse Practitioners, and the Society for Physician Assistants in Pediatrics, among others.

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.

Researchers can obtain a concise analysis of the current state of knowledge of interventions in this field. They will be poised to pursue further investigations that are needed to advance research methods, develop new treatment strategies, and optimize the effectiveness and safety of clinical care for children with this condition.

Methods

In this chapter, we document the procedures that this Evidence-based Practice Center (EPC) used to produce a comparative effectiveness review (CER) on approaches to treatment of infantile hemangioma (IH). These procedures follow the methods outlined in the Agency for Healthcare Research and Quality (AHRQ) Effective Health Care Program *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*.[19]

Topic Refinement and Review Protocol

The topic for this report was nominated by the American Academy of Pediatrics in a public process using the Effective Health Care website. Working from the nomination, we drafted the initial key questions (KQ) and contextual questions (CQ) and analytic framework and refined them with input from key informants representing the fields of pediatrics, dermatology, otolaryngology, vascular anomalies, surgery, and patient advocacy. All members of the research team were required to submit information about potential conflicts of interest before initiation of the work. No members of the review team had any conflicts.

After review from the AHRQ, the questions and framework were posted online for public comment. No changes to the questions or framework were recommended. We also developed population, interventions, outcomes, timing, and settings (PICOTS) criteria for intervention KQ.

We identified technical experts on the topic to provide assistance during the project. The Technical Expert Panel (TEP), representing the fields of pediatrics, pediatric dermatology, otolaryngology, surgery, vascular anomalies, hematology/oncology, and pediatric cardiology, contributed to the AHRQ's broader goals of (1) creating and maintaining science partnerships as well as public-private partnerships and (2) meeting the needs of an array of potential users of its products. Thus, the TEP was both an additional resource and a sounding board during the project. The TEP included seven members serving as technical or clinical experts. To ensure robust, scientifically relevant work, TEP members participated in conference calls and discussions through e-mail to:

- Help to refine the analytic framework and KQ at the beginning of the project; and
- Discuss inclusion/exclusion criteria..

The final protocol was posted to the AHRQ Effective Health Care web site and registered in the PROSPERO international register of systematic reviews (ID#: CRD42015015765).

Literature Search Strategy

Search Strategy

To ensure comprehensive retrieval of relevant studies of therapies for children with IH, we used three key databases: the MEDLINE® medical literature database via the PubMed® interface, the Cumulative Index of Nursing and Allied Health Literature (CINAHL®), and EMBASE (Excerpta Medica Database), an international biomedical and pharmacological literature database via the Ovid® interface. Search strategies for Key Questions applied a combination of controlled vocabulary (Medical Subject Headings [MeSH], CINAHL medical headings, and Emtree headings) to focus specifically on management of IH and harms of interventions. We restricted literature searches for Key Questions to studies published from 1982 to the present to reflect the use of more standardized classification schema for IH.[20] We searched the same databases without date restrictions to identify contextual information.

We only included studies published in English as a review of non-English citations retrieved by our MEDLINE search identified few studies of relevance. Appendix A lists our search terms and strategies and the yield from each database for both Key and Contextual Questions. Searches were last executed in November 2014**.**

We carried out hand searches of the reference lists of recent systematic reviews or meta-analyses of therapies for IH. The investigative team also scanned the reference lists of studies included after the full-text review phase for additional studies that potentially could meet our inclusion criteria.

Grey Literature

AHRQ's Scientific Resource Center requested Scientific Information Packets (SIPs) from companies that produce medications for management of infantile hemangioma (e.g., beta-blockers including propranolol, atenolol, and timolol; corticosteroids including prednisolone and dexamethasone; imiquimod; interferon-alpha-2b; captopril; bleomycin; vinblastine; sodium tetradecyl sulfate; becaplermin); and devices for IH including pulsed dye lasers, Argon lasers, and neodymium yttrium aluminum garnet (Nd:YAG) lasers and searched for regulatory data for medications. We also searched ClinicalTrials.gov to assess reporting bias and to identify any study results that may not have been identified in our other database searches. We also searched the web sites of relevant organizations and associations (e.g., American Academy of Pediatrics, Vascular Birthmarks Foundation) to identify relevant contextual information. We searched the U.S. Food and Drug Administration web site and package insert data for information on harms of medications for IH.

Inclusion and Exclusion Criteria

Table 1 lists the inclusion/exclusion criteria we used based on our understanding of the literature, key informant and public comment during the topic-refinement phase, input from the TEP, and established principles of systematic review methods. We limited our searches for comparative effectiveness questions to studies published in English and from 1982 to the present for studies of the effectiveness of treatments. 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. We included studies with populations including individuals over age 18 if the majority of the participants were under age 18 or the mean age range was within 0 to 18 years. 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 following those agents. 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 1. 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	<u>Admissible designs</u> 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 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) • 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

Once we identified articles through the electronic database searches and hand-searching, we examined abstracts of articles to determine whether studies met our criteria. Two reviewers separately evaluated the abstracts of studies identified in our searches for Key Questions for inclusion or exclusion, using an Abstract Review Form (Appendix B). If one reviewer concluded

that the article could be eligible for the review based on the abstract, we retained it. Following abstract review, two reviewers independently assessed the full text of each included study using a standardized form (Appendix B) that included questions stemming from our inclusion/exclusion criteria. Disagreements between reviewers were resolved by a senior reviewer. Reviewers could flag studies that potentially addressed a Contextual Question identified in the screening process for Key Questions.

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

All abstract and full text reviews were conducted using the DistillerSR online screening application (Evidence Partners Incorporated, Ottawa, Ontario). Appendix C includes a list of excluded studies and the reasons for exclusion. Data extracted for each study are available via the Systematic Review Data Repository (http://srdr.ahrq.gov/).

Data Extraction

The staff members and clinical experts (including one otolaryngologist, one pediatric hematologist/oncologist, one pediatrician, one nurse practitioner, and two epidemiologists) who conducted this review jointly developed the data extraction forms for the Key Questions. We designed form to provide sufficient information to enable readers to understand the studies and to determine their quality; we gave particular emphasis to essential information related to our key questions. We used two templates to facilitate the extraction of data based on study type; one form was designed for case series that reported harms data and one to accommodate all types of comparative studies for effectiveness and harms data.

The team was trained to extract data by extracting several articles into the template and then reconvening as a group to discuss the utility of the template. We repeated this process through several iterations until we decided that the templates included the appropriate categories for gathering the information contained in the articles and for potential meta-analyses. Team data extractors shared the task of initially entering information into the evidence tables. A second team member also reviewed the articles and edited all initial table entries for accuracy, completeness, and consistency. A senior reviewer reconciled disagreements concerning the information reported.

The full research team met regularly during the article extraction period and discussed issues related to the data extraction process (e.g., determining instances of IH vs. other lesions). In addition to outcomes related to imaging or intervention effectiveness (sensitivity and specificity, change in lesion size, resolution, aesthetic appearance, ulceration, vision changes, quality of life), we extracted all data available on harms. Harms encompass the full range of specific negative effects, including the narrower definition of adverse events.

Data Synthesis

We summarized data for Key Questions qualitatively using summary tables where meta-analyses were not possible. We provided a narrative summary of relevant papers for contextual questions.

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: propranolol, triamcinolone, timolol, and oral steroid.

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, either for entire study arms or for individual patients within study arms. In order to incorporate as many quality studies as possible, by minimizing the number excluded due to technical constraints on statistical integration, 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, thereby maximizing the power for estimating parameters precisely. The estimands of interest were the expected proportion of clearance for each intervention agent, along with associated posterior uncertainty. A full description of the meta-analytic methods is reported in Appendix D.

Quality (Risk of Bias) Assessment of Individual Studies

We used separate tools appropriate for specific study designs to assess quality of individual studies meeting eligibility criteria for our Key Questions: questions adapted from the RTI item bank to assess randomized controlled trials (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]

Questions from the RTI item bank evaluate domains including selection bias, performance bias, attrition bias, detection bias, and reporting bias. We used the Newcastle-Ottawa Quality Assessment Scale to assess the quality of nonrandomized studies. It assesses three broad perspectives: the selection of study groups, the comparability of study groups, and the ascertainment of either the exposure or outcome of interest for case-control or cohort studies, respectively. The QUADAS tool considers questions related to participant characteristics, comparisons with a gold standard, and interpretation of the screening test. The harms assessment tool addresses questions related to pre-specification and reporting of harms.

Quality assessment of each study was conducted independently by two team members using the forms presented in Appendix B. Any discrepancies were adjudicated by the two team members or a senior investigator. Investigators did not rely on the study design as described by authors of individual papers; rather, the methods section of each paper was reviewed to determine which rating tool to employ, and we used the algorithm in Appendix E to aid in determining study design. The results of these tools were then translated to “good,” “fair,” and “poor” quality ratings as described below. Appendix F reports quality scoring for each study. We did not assess the quality of papers identified for Contextual Questions.

Determining Quality Ratings

- We required that RCTs receive a positive score (i.e., low risk of bias for RCTs) on roughly 80 percent (11 of 13) of the questions used to assess quality to receive a rating of good/low risk of bias. RCTs had to receive eight to ten positive scores to receive a rating of fair/moderate risk of bias, and studies with ≤ seven positive ratings were considered poor quality/high risk of bias. We considered a score of "unclear" for a question as a negative score. We assessed the risk of bias for each major outcome of relevance reported but report an overall assessment unless the risk of bias varied by outcome.
- We required that cohort studies receive positive scores (stars) on all elements, including use of blinded outcome assessors, and be prospective to receive a rating of good, ≤ 2 negative ratings for fair, and > 2 negative scores for a rating of poor quality.
- For imaging studies we required that studies receive positive scores on all questions to receive a rating of good. We considered studies with ≤ three negative ratings as fair quality and those with more than four as poor quality.
- We required that studies assessed for harms reporting receive at least 3.5 of a possible four points available to receive a rating of "good." We gave partial points to studies that reported monitoring for changes in blood pressure, heart rate, or hypoglycemia. Studies with 2.5 to three positive responses were considered fair quality and those with ≤ two positive responses were deemed to be poor quality.

Strength of the Body of Evidence

We applied explicit criteria for rating the overall strength of the evidence for each key intervention-outcome pair for which the overall risk of bias was not overwhelmingly high. We planned to rate the strength of the evidence for the final outcomes of interest for our Key Questions (Figures 1-3) and for clinically important harms. We used established concepts of the quantity of evidence (e.g., numbers of studies, aggregate ending-sample sizes), the quality of evidence (from the quality ratings on individual articles), and the coherence or consistency of findings across similar and dissimilar studies and in comparison to known or theoretically sound ideas of clinical or behavioral knowledge.

The strength of evidence evaluation that we used is described in the Effective Health Care Program's *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*[19] and in the updated strength of evidence guide,[25]which emphasizes five major domains: study limitations (low, medium, high level of limitation), consistency (inconsistency not present, inconsistency present, unknown or not applicable), directness (direct, indirect), precision (precise, imprecise), and reporting bias. Study limitations are derived from the quality assessment of the individual studies that addressed the KQ and specific outcome under consideration. Each key outcome for each comparison of interest is given an overall evidence grade based on the ratings for the individual domains.

The overall strength of evidence was graded as outlined in Table 2. Two senior staff members independently graded the body of evidence; disagreements were resolved as needed through discussion or third-party adjudication. We recorded strength of evidence assessments in tables, summarizing results for each outcome. We considered case series in the assessment of strength of the evidence for harms.

Table 2. Strength of evidence grades and definitions*

Grade	Definition
High	**We are very confident that the estimate of effect lies close to the true effect for this outcome.** The body of evidence has few or no deficiencies. We believe that the findings are stable, i.e., another study would not change the conclusions.
Moderate	**We are moderately confident that the estimate of effect lies close to the true effect for this outcome.** The body of evidence has some deficiencies. We believe that the findings are likely to be stable, but some doubt remains.
Low	**We have limited confidence that the estimate of effect lies close to the true effect for this outcome.** The body of evidence has major or numerous deficiencies (or both). We believe that additional evidence is needed before concluding either that the findings are stable or that the estimate of effect is close to the true effect.
Insufficient	**We have no evidence, we are unable to estimate an effect, or we have no confidence in the estimate of effect for this outcome**. No evidence is available or the body of evidence has unacceptable deficiencies, precluding reaching a conclusion.

* Excerpted from Berkman et al. 2014[25]

Applicability

We assessed the applicability of findings reported in the included literature addressing our Key Questions 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.

Peer Review and Public Commentary

Researchers and clinicians with expertise in managing IH and individuals representing stakeholder and user communities will provide external peer review of this report; AHRQ and an associate editor will also provide comments. The draft report will be posted on the AHRQ Web site for 4 weeks to elicit public comment. We will address all reviewer comments, revise the text as appropriate, and document changes and revisions to the report in a disposition of comments report that will be made available 3 months after AHRQ posts the final review on the AHRQ Web site.

Results

We present results for Contextual Questions (CQ) followed by those for Key Questions (comparative effectiveness questions). We identified 419 publications potentially relevant to the CQ in our database searches. We also flagged studies for potential relevance to CQ in our screening of studies for Key Questions. We included 50 studies in the narrative summary of information addressing CQ.

CQ1. Natural History of Untreated IH and Adverse Outcomes of Untreated IH

Natural History of IH

IH have been estimated to occur in around 5 percent of neonates and infants.[1] IH may be classified into subtypes including localized, segmental, indeterminate, and multifocal. Several studies have shown most IH to be of the localized type, and regardless of type, most IH involute with time.[26-28] IH usually present within the first month of life and undergo proliferation over the first several months of life. One study found that IH reached 80 percent of their final size by 5 months of age.[29] Segmental IH are more likely to have later growth, defined as after 9 months of age.[29, 30] Involution typically starts by 1 year of age and has been noted to cease around 3.5 years of age.[31, 32] In one large retrospective review of 1109 referred patients (median age=8 months) conducted in the pre-propranolol era, 769 were returned to the care of their primary provider without subspecialty followup, and only 102 (9%) required intervention.[33]

Most lesions resolve by age 5 to 7,[34] but cosmetic deformities may remain.[18, 31] In studies of referred populations, residual lesions (e.g., telangiectasias, atrophy, fibrofatty tissue, hypopigmentation) have been reported in 25 to 69 percent of untreated IH.[31, 35] Lesions affecting visual cortex development may result in lasting deficits in vision even after resolution of the IH.[36]

Indications for Treatment

The major indications for treatment of IH include risks of ulceration, disfigurement, and functional impact.[32, 37, 38] While psychological impact on the child also plays a role in treatment decisions, data on the effects of IH on quality of life for the child have indicated minimal impact. Such data are often limited by the necessity of parent-report in this young population.[18, 39, 40] Estimates of complications from IH vary but are generally noted to occur in approximately 30 percent of the studied population.[27, 28, 41] One study found higher initial complication rates for patients referred to a surgical center, potentially due to the higher likelihood of more advanced lesions being referred.[42] Given that the literature typically includes children treated at referral centers, it is likely that the overall complication rate may be higher in study populations than in the general population.

Risk of complication is generally related to the size of lesions, location of lesions, and/or subtype.[15, 27] Larger lesions are more likely to have complications. One study found a 5 percent increased rate of complications for every 10 cm^2 increase in size (OR 1.051, $p<0.05$).[27] Lesions on the face and perineal regions have the highest rates of complications.[26, 27] Segmental lesions typically have a higher overall complication risk,[26] though at least one study reported a lack of association with complications.[43] Even after controlling for lesion size, segmental subtype

lesions were eleven times more likely to have an associated complication and required treatment eight times more often than other subtypes in one study.[27]

Ulceration is the most common complication leading to intervention, with incidence estimated to range from 7 to 25 percent.[10, 27, 28, 33, 44] Large size is related to increased risk of ulceration, while white discoloration to the lesion was premonitory of ulceration in one study.[42, 45] Ulceration may occur due to mechanical breakdown and outgrowing vascular supply. Ulceration typically occurs later in the proliferation phase and segmental lesions and those in the anogenital, neck, or oral areas are at increased risk.[37]

Location of IH may also influence the decision to treat. Due to the delicate nature of the nasal framework, nasal tip IH can lead to structural complications even after complete resolution, including bulbous tip, tip ptosis, alar notching, splayed alar cartilage and asymmetry. Facial IH are at risk for increased residual skin changes even after involution and concern for long-term poor cosmesis is an indication for treatment. Visual complications such as amblyopia or vision loss have been noted in roughly 7 to 40 percent of periorbital lesions.[27, 28, 46] Size of periorbital lesion is predictive of amblyopia risk and nasal location increases the disturbance risk compared to other periorbital locations.[46, 47]

Airway compromise is another functional disturbance that creates a need for intervention. For patients with airway IH, the degree of obstruction is the best predictor of need for intervention. Unilateral subglottic IH had a lower risk for intervention when compared to circumferential lesions in one report.[48] For patients with cutaneous IH in the beard region, the finding of a subglottic hemangioma has been shown to increase with bilateral involvement.[37, 49]

Half of the infants with cutaneous lumbosacral IH were found to have intraspinal involvement, including occult spinal dysraphism (OSD), found on MRI screening in one recent study.[50] In 17 percent of patients with known OSD, a midline lumbosacral cutaneous hemangioma was observed in another study.[51]Hepatic IH are associated with arteriovenous shunting and high output cardiac failure (0.4%) and were more likely to undergo treatment if signs of congestive heart failure were present in two studies.[27, 52] Extensive liver involvement is also associated with hypothyroidism, but the need for treatment of asymptomatic liver IH varies; in one study, for example, 8 percent of children required treatment[53] while 50 percent of children in another had treatment for the IH or associated complications including hypothyroidism or cardiac failure.[54]

PHACE syndrome (Posterior fossa malformations, arterial anomalies, cardiac defects, eye abnormalities, sternal cleft, and supraumbilical raphe) has been identified in 19.7 percent to 30 percent of infants with large segmental facial IH.[55, 56] Larger lesions and involvement of more than one facial segment were found to be increased risk factors for PHACE.[56] Children with PHACE are at greater risk for IH-related complications such as ulceration or visual impairment and generally require treatment for IH. Propranolol has been used in this population, and investigators developed methods for risk stratification to determine the appropriateness of beta-blockers.[57, 58] Other syndromes may be associated with segmental IH in the perineal or lumbosacral regions (LUMBAR [lower body hemangioma and other cutaneous defects, urogenital anomalies, ulceration, myelopathy, bony deformities, anorectal malformations, arterial anomalies, and renal anomalies], PELVIS [perineal hemangioma, external genitalia malformations, lipomyelomeningocele, vesicorenal abnormalities, imperforate anus, and skin tag] and SACRAL [spinal dysraphism, anogenital, cutaneous, renal, and urologic anomalies, associated with an angioma of lumbosacral localization]) and may require treatment of the IH to avoid functional or cosmetic sequelae.[59, 60]

CQ2. Evidence for Association of Cutaneous IH and Occult IH

Overall, limited literature addresses the association of a higher number of cutaneous IH and extracutaneous IH. Some data from case series suggest 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. One study addressed associations with IH in the spinal area and reported that nine of 48 children with cutaneous IH on the lumbosacral skin had intraspinal lesions (19%), though the study did not report the number of cutaneous lesions. We summarize studies addressing hepatic and airway IH below.

Evidence for the association of a greater number of cutaneous IH with hepatic IH comes primarily from case series including 371 infants with IH.[53, 54, 61-63] In one retrospective series, investigators analyzed data from 26 children with hepatic IH (presentation of IH at birth or up to 4 months of age).[54] Among the 26, 18 also had multiple or diffuse cutaneous lesions (69%) and underwent imaging, and 15 of 18 had multiple or diffuse liver IH. Investigators classified the liver IH as focal (n=8 children), multifocal (n=12 children), or diffuse (n=6 children). Among children with focal lesions, three had multiple cutaneous IH, two had a single cutaneous IH, and three had no cutaneous IH. In the multifocal group, 11 of 12 children had multiple cutaneous lesions (mean 14.25 ± 12.50 lesions) and liver IH. All but one of the 6 children with diffuse hepatic IH had multiple cutaneous lesions. Across lesion types, cutaneous lesions generally resolved before hepatic lesions.

Another series included 37 children, 16 percent of whom had three to five small cutaneous lesions; 43 percent had six or more small cutaneous lesions; 16 percent had cutaneous miliary (30-100 pinpoint lesions) lesions; 11 percent had a single large IH; and 14 percent had a combination of a large and one or more small cutaneous IH.[61]Eight of 37 (22%) children had concurrent hepatic IH. Children with cutaneous miliary IH had a greater number of hepatic IH (n=7 to 35) than did infants with other cutaneous patterns. Another retrospective series reported that 17 of 23 infants (53%) with hepatic IH had multiple (≥5) cutaneous IH.[63]

In another retrospective series of children seen at referral centers, 62 children had six or more cutaneous IH or one large (≥5 cm) cutaneous IH and seven had three to five small (<5 cm) cutaneous IH. Fifteen of the 69 children (22%) had liver IH (14/62 with 6 or more or 1 large cutaneous and 1/7 with 3-5 small lesions).[62] Forty-five percent of children with miliary cutaneous IH (n=5/11) had hepatic IH, and all five had multiple, small, widespread hepatic IH on ultrasound. Six of 69 children also had other visceral involvement: five with cervicofacial IH had airway IH (2 of these had concurrent hepatic IH) and one had concurrent hepatic IH and bladder IH. Hepatic lesions regressed earlier than cutaneous in four out of nine children with followup hepatic ultrasounds; lesions regressed concurrently in three children, and in two children, cutaneous lesions regressed earlier than hepatic.

In a prospective case series including 201 infants between 0 and 6 months of age with IH seen at specialty pediatric dermatology clinics, 24 of the 151 (16%) infants with at least five cutaneous IH had hepatic IH, while none of the children with one to four IH had hepatic involvement (p=0.003).[53] Preterm birth (< 37 weeks gestation) and lower birth weight were associated with having five or more cutaneous IH (p values <.05, OR for 5 or more cutaneous IH after preterm birth=4.5, 95% CI: 1.45 to 14.25). There was no significant association between the number of cutaneous IH and the number of hepatic IH, and two children with 5 or more cutaneous IH but without hepatic IH had airway or gastrointestinal IH. Other reports have also noted liver IH occurring in conjunction with multiple cutaneous IH.[5, 64-67]

Case series have also reported on the association between cutaneous IH, particularly on the face, and airway IH. In one report including 187 children with IH on the face and neck, 16 (8.5%) had lesions with a beard distribution.[49] Ten of these 16 (63%) had symptomatic airway IH, and four of these required tracheostomy. In another case series of 25 children, seven had bilateral cutaneous IH of the head and neck, and three of these (43%) had airway IH.[36] In one large series including 1226 children with cutaneous IH, 108 had segmental lesions and 56 of these had lesions in a beard distribution pattern on at least one side of the face.[68]Sixteen of these 56 (29%) had concurrent upper airway IH, also with a segmental distribution.

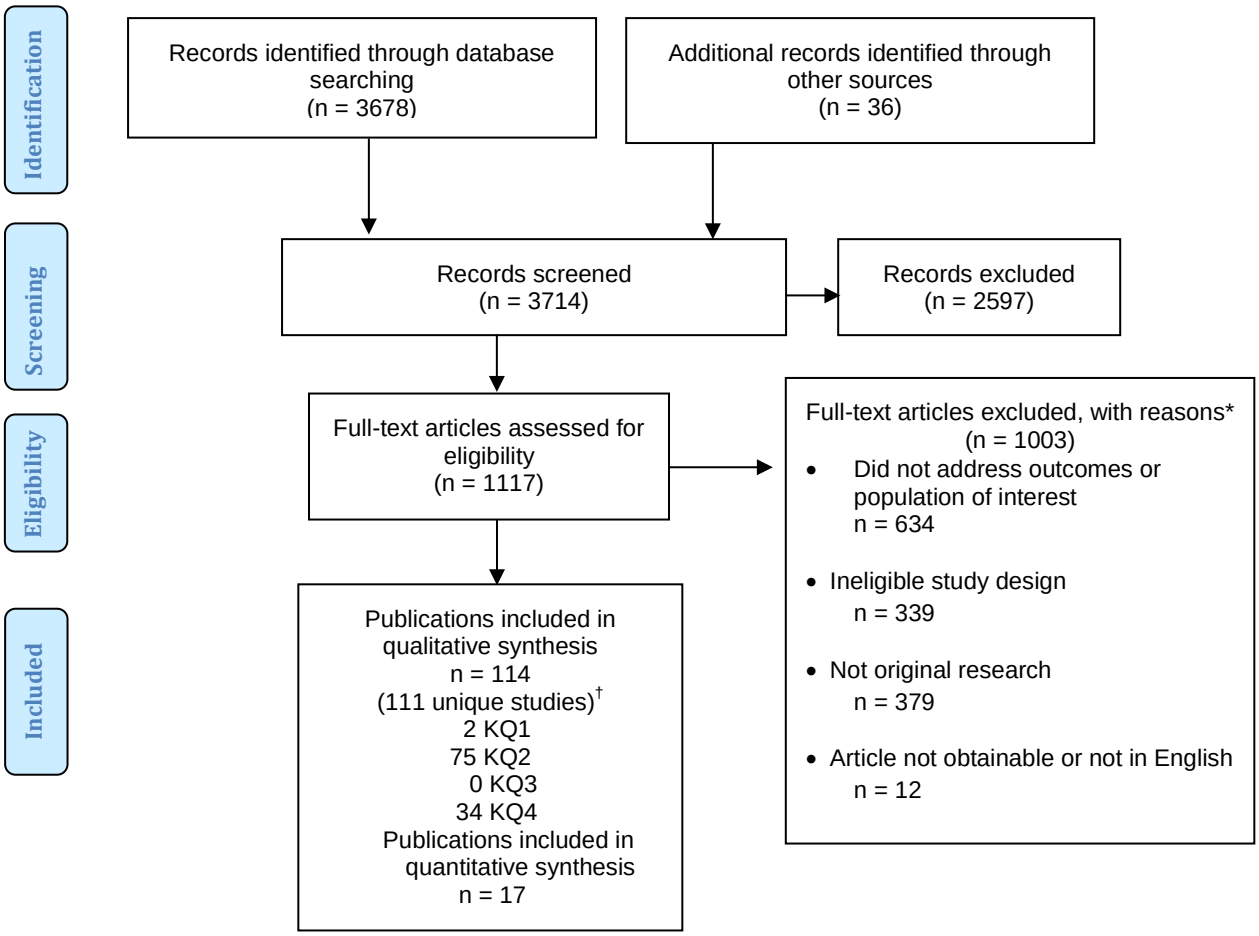
Another retrospective case series assessed 342 children with IH on the upper or lower lips.[69] Two-hundred thirteen children had focal lesions, and 129 had segmental, nearly 50 percent of these had unilateral or bilateral mandibular lesions. Thirty children (24 with V3 distribution) had concomitant airway IH, also in a segmental distribution. One child had PHACES syndrome. No children with focal lesions had airway IH.

In another series of 31 infants with subglottic IH, 20 had concomitant cutaneous IH, but the study did not assess the association with specific numbers of lesions or anatomic region.[70] Over half of cutaneous lesions were on the head or neck. Children with cutaneous IH had more accurate diagnosis of airway IH (correct in 14/20 cases compared with 1/10 cases of airway IH without cutaneous IH, $p=0.03$) and with longer duration of tracheostomy (575 vs. 295 days, $p=0.05$).

Results of Literature Searches for Key Questions

We identified 3714 nonduplicative titles or abstracts with potential relevance, with 1117 proceeding to full text review (Figure 4). We excluded 1003 studies at full text review. We included 111 unique studies (114 publications) in the review. Among these 111 studies, 34 comparative studies addressed the effectiveness and harms of therapies, and 77 case series provided data on harms only. We present findings by intervention under each key question.

Figure 4. Disposition of studies identified for this review



†Numbers next to each Key Question indicate number of unique studies addressing the question. Studies could address more than one Key Question. Neither study identified for KQ1 addressed harms. Of the 75 studies identified for KQ2, 22 addressed benefits and harms, 1 addressed only benefits, and 52 addressed only harms. Of the 34 identified for KQ4, 9 addressed benefits and harms, and 25 addressed only harms.
*Numbers do not tally as studies could be excluded for multiple reasons.
Abbreviations: KQ = key question; n = number.

Description of Included Studies

The 111 unique studies addressing Key Questions comprise 12 randomized controlled trials (RCTs), five prospective and 15 retrospective cohort studies, two diagnostic accuracy studies (defined as studies that compared the accuracy of imaging modalities in identifying or characterizing infantile hemangioma [IH]), and 77 case series (used for harms data only). Most studies were conducted in Europe (n = 35) or the United States or Canada (n = 35). Thirty-one were conducted in Asia and 10 in other countries including Australia, Egypt, and Chile. (Table

3). Thirty-four comparative studies reported effectiveness outcomes. We considered six of these studies to be good quality, 18 fair quality, and 10 poor quality. One-hundred and eight studies (comparative studies and case series) reported harms/adverse events data. We considered 14 of these as good quality for harms reporting, two as fair quality for harms reporting, and the remainder (n = 92) as poor quality for harms reporting. Most studies addressed beta-blockers (n = 57); 21 addressed lasers; 18 addressed steroids; 13 addressed surgical approaches; and two addressed diagnostic modalities.

We included 17 studies in a network meta-analysis. All studies addressed pharmacologic agents and included four RCTs and five cohort studies evaluating propranolol and placebo or observation or another active agent,[13, 71-78] one RCT and one cohort study comparing propranolol and other beta-blockers,[79, 80] three cohort studies and one RCT assessing timolol compared with placebo or observation or another agent,[81-84] and one RCT and one cohort study evaluating different steroids.[85, 86]

Table 3. Characteristics of included studies addressing effectiveness and harms

Characteristic	RCTs	Prospective Cohort Studies	Retrospective Cohort Studies	Diagnostic Studies	Case series*	Total Literature
Intervention						
Corticosteroid	3	0	1	0	14	18
Beta-Blocker**	6	5	8	0	38	57
Laser	3	0	6	0	12	21
Surgery	0	0	0	0	13	13
MRI or ultrasound	0	0	0	2	0	2
Population Characteristics						
Anatomic location of IH						
Multiple	12	4	12	1	66	95
Periocular	0	1	1	0	5	7
Airway	0	0	1	0	1	2
Oral/Maxillary	0	0	0	0	3	3
Parotid	0	0	0	0	1	1
Lumbosacral	0	0	0	1	0	1
Nasal	0	0	1	0	1	2
Study population						
U.S./Canada	2	1	7	2	23	35
Europe	3	0	6	0	26	35
Asia	3	3	2	0	23	31
Other	4	1	0	0	5	10
Outcomes Reported						
Resolution/Clearance-related	12	7	10	0	0	29
Vision	1	2	1	0	0	4
Quality of life	2	0	1	0	0	3
Number treatments/invasive treatments needed	1	0	5	0	0	6
Diagnostic accuracy	0	0	0	2	0	2
Rebound growth	4	1	5	0	0	10
Harms	12	6	13	0	77	108
Total N participants	**1013**	**230**	**992**	**96**	**8193**	**10524**

*Case series reported other outcomes; however, we only extracted harms data from case series for this review.

**Studies that compared a beta-blocker to another beta-blocker or placebo/observation or to another active comparator such as steroids, other agents, or laser are reported only in this row.
Abbreviations: n = number; RCT = randomized, controlled trial

Grey Literature

In response to 21 requests for Scientific Information Packets, we received four documents, all of which addressed medications (becaplermin gel, recombinant interferon alfa-2b) that were not evaluated in studies meeting our criteria. The documents yielded no citations of relevance for this review, and the documents themselves did not meet criteria for inclusion in the review (one case series of 8 individuals, one addendum to an article, two files of prescribing information). Our search of ClinicalTrials.gov did not yield any results not identified in our other searches, and our searches of the web sites of relevant organizations yielded background information for informing our contextual questions.

Key Question 1. Effectiveness and Harms of Imaging Modalities

Key Points

- Strength of the evidence (SOE) for the effectiveness of imaging for IH was insufficient given few studies.
- 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.

Overview of the Literature

Two poor quality diagnostic accuracy studies—one prospective[50] and one retrospective[52]—addressed imaging modalities. Both studies were conducted in tertiary care settings with care settings in the United States, Canada, and Spain. One study enrolled patients from nine centers and included patients less than18 years old with IH in the lumbosacral area measuring greater than 2.5 cm.[50] The retrospective cohort study reported chart review data from two tertiary care centers and included 55 patients (mean age of 30 days) with liver IH.[52]

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.

Detailed Analysis

One prospective cohort study involved nine centers and enrolled 48 children with IH in the lumbar-sacral area to receive imaging (MRI or ultrasound) to evaluate for evidence of occult spinal dysraphism (OSD), including intraspinal IH.[50] Seven out of 26 (26.9%) children who underwent ultrasound had an abnormality compared with 21 of the 41 (51.2%) patients who received MRI and were noted to have a spinal abnormality. Nineteen of these patients underwent both ultrasound and MRI. In five cases ultrasound did not reveal an abnormality later found on MRI. Agreement between ultrasound and MRI was 0.27 (95% CI: -0.15 to 0.7, p=0.21), which

was consistent with chance. 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 IH specifically: assuming a false positive value of 0, ultrasound, which missed 4 intraspinal IH in 26 scans, 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%).

Children with another cutaneous finding (e.g., gluteal cleft, skin tag) in addition to the IH were noted to have increased risk of OSD. These findings are limited by the arbitrary selection of the 2.5 cm cut-off for inclusion. Radiology results were also reviewed by radiologists at the individual centers, and inter-reader reliability could not be ascertained. The ultrasound screening was completed at some centers as part of screening younger infants and was not simultaneous with MRI.

The retrospective cohort study reported results from a chart review of 55 patients with hepatic IHs.[52] All imagining studies were reviewed by four radiologists, and 46 of the 55 participants underwent more than one imaging modality. Ultrasound was commonly used as the first technique and identified lesions in 42 of 44 patients (sensitivity of 95%). Ultrasound identified direct shunts in 9 of 10 patients with shunts identified by angiography. Children with findings of congestive heart failure or aortic tapering on imaging were more likely to require intervention for their hepatic lesion. This study is limited by small sample size, retrospective design that allowed only for existing imaging, and study time frame of 20 years during which quality of imaging likely improved.

Key Question 2. Effectiveness and Harms of Corticosteroids or Beta-Blockers

Network Meta-Analysis of the Effectiveness of Pharmacologic Agents

Full and detailed methods and results of the meta-analysis are available in Appendix H. Effect measures (Table 4) reflect effects on the logit scale and are not immediately clinically interpretable, but they demonstrate the superiority of beta-blockers. Specifically, oral propranolol had the highest effect size.

Table 4. Posterior estimates of effect size

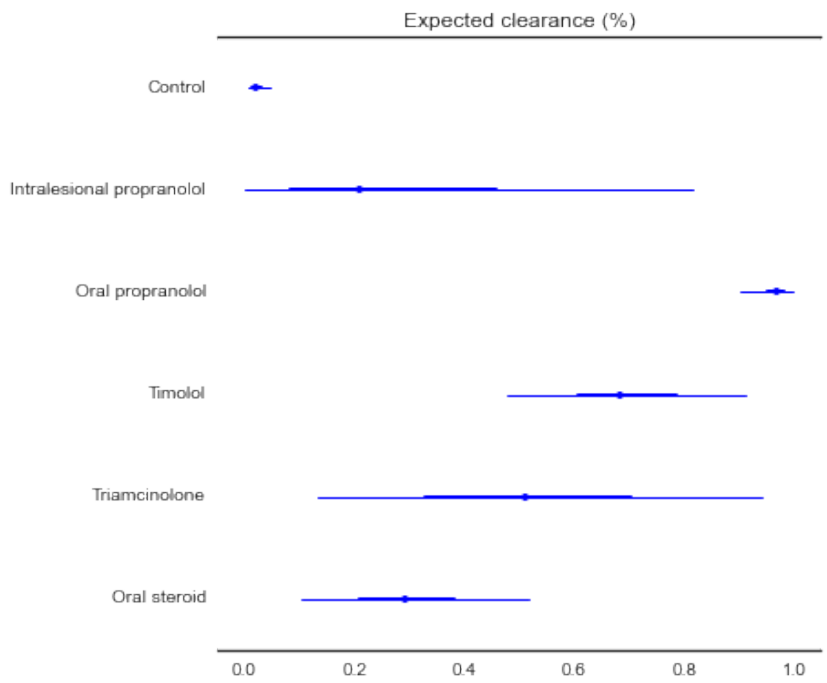
Agent	Mean	Standard Error	95% Credible interval	
Oral propranolol	7.1	0.8	5.6	8.4
Topical timolol	4.5	0.6	3.0	5.6
Intralesional triamcinolone	4.0	1.3	1.3	6.4
Oral steroid	2.9	0.4	2.1	3.9

Note: Table illustrates posterior estimates of effect size, on logit scale, relative to control, along with standard error and 95% credible interval. Positive values indicate increased clearance relative to control, negative indicate decreased clearance.

More clinically interpretable are the clearance rates, presented in Figure 5, which presents mean expected clearance rates and our confidence bounds around the estimates. The expected efficacy of control arms was estimated to be 2 percent (95% BCI: 0% to 5%), i.e., we would expect to see, on average, 2 percent clearance of IH in children who receive placebo or no treatment during the study period. All non-control treatments were estimated to have a larger expected clearance than control (Figure 5).

The largest mean estimate of clearance was for oral propranolol (95%, 95% BCI: 86% to 100%). Clearance associated with the use of oral steroids was 29% (95% BCI: 9% to 50%), thus providing a clearance rate intermediate to control and use of beta-blockers. Triamcinolone, an intralesional injectable steroid, had a comparable clearance rate to oral steroids. Few data were available for intralesional propranolol, which is reflected in its larger credible interval.

Figure 5. Estimates of expected IH clearance



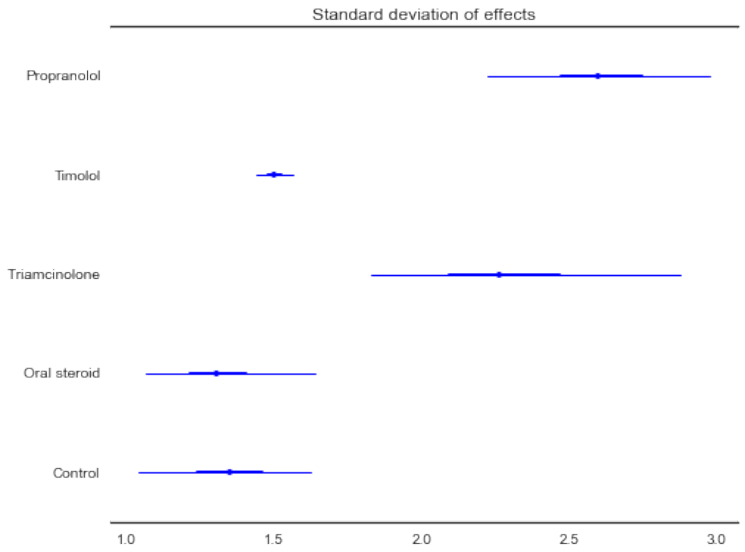
Note: Estimates of expected IH clearance are expressed as percent clearance relative to initial condition for each treatment, along with associated posterior interquartile range (thick lines) and 95% credible interval (thin lines).

Figure 6 represents the variability in effects seen across the patient populations in terms of percent clearance. Propranolol was estimated to have the largest variability in clearance rate with some patients experiencing much greater clearance than others (σ=2.6, 95% BCI: 2.2 to 2.9) though triamcinolone obtained a very similar estimate (σ=2.3, 95% BCI: 1.9 to 2.9). This may be a reflection of the heterogeneity of the study population in terms of types and severity of IH.

Oral steroids were estimated to be the least variable (σ=1.1, 95% BCI: 1.4 to 1.6), followed by timolol (σ=1.5, 95% BCI: 1.4 to1.6). Although the estimate of effect was lower, there was substantially less variation in what might be expected clinically with steroid treatments.

Because of relatively sparse information from several treatment agents, we were unable to separately estimate variance parameters for all of the interventions, and instead fit a simplified model that assumed variances were equal. To check the validity of this assumption, we also fit a model on the subset of interventions with sufficient numbers of studies (>3) to estimate variance parameters, and noted that the variance estimates ranged from 1.3 (1.1 to 1.6) to 2.6 (2.2 to 2.9) on the logit scale. This was reasonably close to the 1.6 (1.5 to 1.7) estimated as the pooled variance.

Figure 6. Estimates of the variation of each treatment



Note: Estimates of the variation of each treatment are expressed as standard deviation, along with associated posterior interquartile range (thick lines) and 95% credible interval (thin lines).

Effectiveness and Harms of Corticosteroids

Key Points

- In our network meta-analysis, oral steroids had a clearance rate of 29 percent (95% Bayesian credible interval [BCI]: 9% to 50%), and the rate for intralesional triamcinolone was 53 percent (95% BCI: 14% to 97%) compared with 2 percent (95% BCI: 0% to 5%) for placebo or observation (moderate SOE for improvement in IH with oral steroids vs. observation or placebo; low SOE for greater effectiveness of intralesional steroids vs. observation or placebo). This means that we would expect to see, on average, 29 percent clearance of IH in children receiving oral steroids.
- Steroids studied varied in dose, type, and route of administration.
- Children in treatment arms typically experienced reductions in lesion size, but outcomes across studies are difficult to compare given differences in scales.
- Harms were varied and frequently included Cushingoid facies, irritability/mood changes, growth retardation, and skin atrophy or depigmentation. Ulceration was frequently reported in studies of intralesional steroids. SOE was moderate for the association of steroids with clinically important harms.

Overview of the Literature

We identified 18 studies (three RCTs, one cohort study, and 14 case series) reporting outcomes and/or harms following corticosteroid use in children with IH.[33, 85-101] One RCT and one case series[99, 101] likely report on a subset of the same children; however, the extent of overlap is not clear. Three RCTs[85, 86, 101] and one retrospective cohort study[33] addressed corticosteroids and included a total of 239 children (age range 1-72 months) with IH in multiple anatomic sites. Studies were conducted in India,[101] Canada,[85] Pakistan,[86] and Turkey.[33] Two studies included children with cutaneous IH, and IH types across all studies included superficial, deep, and mixed.

Studies assessed oral methylprednisolone, oral prednisolone, intravenous methylprednisolone, topical mometasone furoate, and intralesional triamcinolone acetonide and compared one agent to another or various doses of agents. One RCT included an observational/conservative control group.[86] Only one RCT explicitly noted that assessors were blinded to treatment status.[85] Other outcomes assessed include rebound growth, color/texture change, vision changes, and adverse events. Treatment duration (where clearly reported) in comparative studies ranged from 3 weeks to 12 months. We rated one RCT as good,[85] one as fair,[101] and one as poor[86] quality and the cohort study[33] as fair quality for effectiveness outcomes. We considered the cohort study and one RCT[33, 101] as poor quality for harms reporting and two RCTs as good quality for harms reporting.[85, 86]In our network meta-analysis, oral steroids had a mean estimated expected clearance rate of 29 percent (95% BCI: 9% to 50%). The rate intralesional triamcinolone had a rate of 53 percent but with wide confidence bounds (95% BCI: 14% to 97%).

Thus, there is adequate evidence to support a moderate strength of evidence for oral steroids to have a modest effect on clearance rates and low SOE for intralesional steroids to have a modest (albeit larger) effect relative to control with wide confidence bounds.

We also report harms from one RCT[78] and three cohort studies[75-77] that compared steroids with propranolol (effectiveness outcomes reported in Effectiveness and Harms of Beta-Blockers Compared With Other Active Modalities section below). These studies were conducted in the U.S.,[76, 78] Canada,[75] and Egypt[77] and included 175 children with IH (age range=3.8 to 6.1 months). We rated these studies as good[78] and poor[75-77] quality for harms reporting.

Fourteen case series (four prospective and 10 retrospective) provided harms data on corticosteroids.[87-100] Children in case series (N=3155) ranged in age from 0 to 19 years and typically had IH in multiple anatomic sites. Four case series were conducted in the United States, three in India, two in the U.K., and one each in China, Germany, Israel, Thailand, and the Netherlands. Two studies reported on only orbital or periocular IH.[89, 100] Steroids administered included intralesional triamcinolone or betamethasone (nine studies), oral prednisolone or prednisone (five studies), or an unspecified mix of oral, topical, and intralesional steroids (one study). Some studies reported on use of more than one agent. Treatment duration was frequently not reported. In three studies of intralesional steroids clearly reporting such data, most children required more than one injection to promote clearance, with a maximum of 12 injections reported.[89, 90, 92, 97] We rated all case series as poor quality for harms reporting.

Nonetheless, steroids were consistently associated with clinically important harms including Cushingoid appearance, infection, growth retardation, hypertension, and mood changes that may be important in making treatment decisions. The SOE is moderate for the association of steroids with these clinically important harms.

Detailed Analysis

Effectiveness of Steroids

Intravenous or Intralesional versus Oral Steroids

One good quality RCT conducted at a Canadian tertiary care hospital randomized 20 children with problematic facial IH (defined as causing visual impairment or disfigurement) to oral prednisolone (2 mg/kg/day tapered over 9-12 months, n=10, mean age=11±4 weeks) or monthly IV methylprednisolone (30 mg/kg infused over 1 hour for 3 days for 3 months, n=10, mean age=12±3 weeks).[85] Blinded assessors and parents (unblinded) rated change in size on a -100 to

+100 mm VAS scale (0= no change, - =increase in size, +=decrease in size) using serial photographs. Children in the oral steroid group had greater improvement in size at both the 3-month post-treatment and first birthday followup timepoints (median VAS of 70 in oral group compared with 12 in IV group, p=0.002 and median VAS of 50 in oral group vs. -1.5 in IV group, p=0.005). Vision improved in six of the eight children with eye involvement (2 in oral group and 4 in IV group), and seven children in the oral group and six in the IV group required additional steroids due to rebound growth or lack or response. In combined group analyses, children with periorbital involvement had less improvement at both time points (median VAS of 4 vs. 48, p=0.049 at 1 year).

A poor quality RCT conducted in Pakistan compared oral prednisolone (n=25) and intralesional triamcinolone (n=25) and observation (n=25) in children (mean age=5.0±2.9 months) with superficial (73.3%), mixed (20%), and deep (6.6%) cutaneous IH.[86] Investigators assessed reduction in size using a graded scale (1= >50% reduction, 2= <50% reduction, 3= little or no decrease or increase), changes in morphology, and duration of proliferation. Lesion sites varied significantly among groups at baseline (p<0.015). Lesion size decreased significantly (p<0.001) in all three groups, though baseline size measures are not reported. Overall, 19 children had at least 50 percent reduction (8 in prednisolone arm and 11 in triamcinolone arm). Thirty-one children had little or no change (19 in observation arm, 6 in each treatment arm). Morphology changed in 88 percent of the prednisolone group, 92 percent of the triamcinolone group, and 16 percent of the observation group. Differences in morphology were significant between the conservative management group and both treatment groups combined (p<0.005). Proliferation time did not decrease in 88 percent of the observation group (statistically significant vs. the triamcinolone arm, p<0.001). One child in the prednisolone arm had rebound growth. In these two small studies, oral and intralesional steroids were associated with decreases in lesion size. Table 5 outlines outcomes in these studies.

Table 5. Key resolution outcomes in studies comparing intravenous or intralesional and oral corticosteroids

Author, Year Comparison Groups (n) Quality	Age Type	Location	Measures of Resolution/ Response	Resolution Outcomes	Rebound Growth/ Recurrence, n (%) Other Outcomes
Pope et al. 2007[85] G1: Methyl-prednisolone, 30 mg/kg infused over an hour for three days monthly (10) G2: Prednisolone, oral 2/mg/kg/day (10) **Quality:** Good	**Age, mean±SD, weeks** G1: 12 ± 3 G2: 11 ± 4 **Type** All children had mixed, superficial and deep facial IH	G1+G2: Multiple	• 100-mm visual analog scale (0:no change, +:decrease in size, -:increase in size)	**VAS score at 3 months, median (IQR)** G1: 12 (-18 to 39) G2: 70 (54 to 80) G1 vs. G2 p=0.002 **VAS score at 1 year, median (IQR)** G1: -1.5 (-35 to 22) G2: 50 (35 to 67) G1 vs. G2 p=0.005	**Need for additional treatment, n (%)** G1: 7 (54) G2: 6 (46, additional treatment given for regrowth specifically) **Vision outcomes** • Eye involvement in 5 children in G1 and 3 in G2 • No change in eye findings in 1 child in each group at 1 year, and improvement in 4 in G1 and 2 in G2

Author, Year Comparison Groups (n) Quality	Age Type	Location	Measures of Resolution/ Response	Resolution Outcomes	Rebound Growth/ Recurrence, n (%) Other Outcomes
Jalil et al. 2006[86] G1: Triamcinolone 1-5 mg/kg intra-lesional (25) G2: Prednisolone, oral 2/mg/kg/ on alternate days (25) G3: Observation (25) **Quality:** Poor	**Age, mean±SD, months (range)** G1+G2+G3: 5.0 ± 2.9 (1 to 12) **Type** Superficial, % G1+G2+G3: 73.3 Deep G1+G2+G3: 6.6 Combined G1+G2+G3: 20	G1+G2+G3: Multiple	• Grade I greater than 50% reduction in size • Grade II less than 50% reduction in size • Grade III little or no decrease (or increase)	**Lesion size reduction** Grade I G1: 11 G2: 8 G3: 0 Grade II G1: 8 G2: 11 G3: 1 Grade III G1: 6 G2: 6 G3: 19 No change G3: 5	**Rebound growth** G1: 0 G2: 1 G3: 0

Abbreviations: G = group; IQR = interquartile range; SD = standard deviation; VAS = visual analog scale

Intralesional versus Topical Steroids

One fair quality RCT conducted in India randomized children (age range=NR) with less than or equal to two superficial IH of less than 5 cm to daily topical mometasone furoate (n=52) or monthly intralesional triamcinolone (n=47) for 6 to 8 months (Table 6).[101] Patients in this study likely overlap with those described in a retrospective case series,[99] but the extent of overlap is not clear. Investigators graded response to steroids based on cessation of growth, lightening of color, and flattening and considered a positive response in three parameters as "excellent," response in two of three parameters as "good," and response in one parameter as "poor." Forty-five children in each group responded to treatment (mometasone: 50% excellent, 36.5% good, 13.4% poor response; triamcinolone: 63.8% excellent, 31.9% good, 4.2% poor response). Response to steroids did not differ by age or sex.

Table 6. Key resolution outcomes in studies comparing intralesional and topical corticosteroids

Author, Year Comparison Groups (n) Quality	Age, Months Type	Location	Measures of Resolution/Response	Resolution Outcomes
Pandey et al. 2010[101] G1: Mometasone furoate, topical thin film applied twice daily (52) G2: Triamcinolone acetonide, intralesional 1-2 mg/kg (47) **Quality:** Fair	**Age** NR **Type, %** Superficial:100	NR	• Cessation of growth, lightening of color, and flattening of surface • Positive response in all 3 parameters=Excellent • Positive response in 2 parameters=Good • Response in single or no parameter=Poor	**Response rate, n (%)** Excellent G1: 26 (50) G2: 30 (63.8) Good G1: 19 (36.5) G2: 15 (31.9) Poor G1: 7 (13.4) G2: 2 (4.2)

Abbreviations: G = group; IH = infantile hemangioma; n = number; NR = not reported

Methylprednisolone vs. Prednisolone

In one Turkish retrospective cohort study of fair quality, 283 of 1109 children with superficial (53.7%), deep (18.8%), or mixed (16%) IH seen over 23 years at one hospital received either observation (n=238), 2 mg/kg/day prednisolone (n=26, median age at initiation=5 months), 10mg/kg/day methylprednisolone (n=11, median age at initiation=6 months), or methylprednisolone tapered from 30 mg/kg/day to 10 mg/kg/day for 7 days (n=8, median age at initiation=7 months).[33] Investigators assessed response to steroids by considering change in size, color, and texture using a 1 (poor) to 100 (excellent) percent scale and followed participants for a median of 4 (range 1-11) years after treatment. Among the children in the observation group at a median of 2 years of followup, 92 had complete or near complete (75-100%) regression, 37 had 50 to 75 percent regression, 20 had 25 to 50 percent regression, and 89 had less than 25 percent regression. By age 5, 68 percent out of an unstated number of children followed had complete regression, and 90 percent of 92 children followed had complete regression by age 9. Children who received steroids did not differ at baseline in terms of age; sex; or IH type, location, or size. Most lesions (78%) across groups were on the facial region. Overall, 16 children (36%) had a good or excellent response; 15 (33%) had a fair response; and 14 (31%) had poor response. Response did not differ significantly among or between the three groups, but rebound growth was significantly higher (p=0.045) among those receiving methylprednisolone (dose not clearly reported, n=8 with rebound growth) compared with prednisolone (n=4 with rebound growth). Response to steroids was not associated with sex, age, lesion type, size, or location, or age at treatment initiation in univariate analyses. In multivariate analyses, lesion size and age at treatment initiation were significantly associated with treatment response, with smaller lesions associated with better response (response in patients with 0-4 cm lesions vs. 5-9 cm, OR=0.144, 95% CI: 0.23 to 0.907, p=0.0041). Patients with larger lesions (10-15 cm) had the worst response (OR=0.038, 95% CI: 0.003 to 0.533, p=0.015). Younger age at treatment initiation was also associated with better response (OR=0.892, 95% CI: 0.802 to 0.992, p=0.0041). Table 7 outlines resolution outcomes.

Table 7. Key resolution outcomes in studies comparing methylprednisolone and prednisolone

Author, Year Comparison Groups (n) Quality	Age, Months Type	Location	Methods and Measures of Resolution/ Response	Resolution Outcomes	Rebound Growth/ Recurrence, n Other Outcomes
Akyuz et al. 2001[33] G1: Prednisolone, oral 2mg/kg/day (26) G2: Methylprednisolone, oral low dose 10mg/kg/day tapered to 2 mg/kg/day (11) G3: Methylprednisolone, oral low dose 30mg/kg/day tapered to 5 mg/kg/day (8) **Quality:** Fair	**Age, mean (range)** G1: 5 (2-72) G2: 4 (2-11) G3: 6 (1-36) **Type** Capillary, n (%) G1: 11 (42.3) G2: 2 (18) G3: 4 (50) Cavernous (Deep) G1: 8 (30.8) G2: 4 (36.4) G3: 4 (50) Mixed G1: 7 (27) G2: 5 (45.5) G3: 0	G1+G2+G3: multiple	• Change in dimension, lightening of color, and softening of texture • Response graded as: Excellent: 75-100% Good: 50-75% Fair: 25-50% Poor: < 25%	**Response, n (%)** G1+G2+G3: Good or excellent: 16 (36) Fair: 15 (33) Poor: 14 (31) G1 vs. G2 vs. G3: p=ns	**Rebound Growth** G1: 4 G2+G3: 8 G1 vs. G2+G3: p=0.045 **Effect Modifiers** • No significant association between response to treatment and sex, age, lesion type, size, location, and age at treatment initiation in univariate analyses • In multivariate analyses, younger age and smaller lesion size associated with better response

Abbreviations: G = group; n = number

Harms of Steroids

Harms Reported in Studies Included in This Review

Two of four comparative studies that addressed steroids explicitly defined harms and were considered good quality for harms reporting.[85, 86] Another RCT (good quality for harms reporting) that compared prednisolone and propranolol also predefined harms.[78] Studies included a limited number of participants and may not have been adequately powered to detect harms. One RCT that compared harms reported in the prednisolone arm with those reported in the methylprednisolone arm noted no significant differences in harms between groups,[85] as did an RCT comparing prednisolone, triamcinolone, and conservative management.[86] One child receiving oral prednisolone discontinued the study due to persistent vomiting.[85] The final RCT reported harms using a general classification.[78] The frequency of harms between the prednisolone and propranolol groups did not differ significantly (44 vs. 32, respectively), and harms associated with prednisolone included endocrine (n=0.18% of lesions), gastrointestinal (n=0.14% of lesions), growth and development (n=0.23% of lesions), infection (n=0.09% of lesions), metabolic (n=0.02 % of lesions), and pulmonary/respiratory (n=0.11% of lesions). Severe adverse events occurred more frequently in the prednisolone arm (11 vs. 1 in propranolol arm, p=0.01). Nine of the 11 severe events were related to growth restriction. Fewer children in the prednisolone arm had pulmonary events (typically upper respiratory tract infection) compared with children in the propranolol group (5 vs. 14, p<0.001). Five of eight participants

receiving prednisolone discontinued due to adverse events, and study enrollment was stopped due to adverse events.[78]

One cohort study (poor quality for harms reporting) did not report precise harms data but noted that 20 of 45 children receiving either prednisolone or moderate or high dose methylprednisolone developed Cushingoid facies, and 16 of 45 developed irritability, both of which resolved upon cessation of the drug.[33] Three cohort studies (effectiveness outcomes reported in Effectiveness and Harms of Beta-Blockers Compared With Other Active Modalities section below) comparing oral or intralesional steroids with oral or intralesional propranolol reported harms including irritability, Cushingoid features, and hypertension.[75, 76] One study of intralesional triamcinolone reported that no adverse events occurred.[77] Harms frequently reported across all comparative studies addressing steroids included irritability, crying, pain, Cushingoid appearance, and skin depigmentation (Table 8).

Serious harms included two cases of respiratory distress requiring hospitalization in children receiving either prednisolone or methylprednisolone.[85] A child receiving prednisolone also developed uncomplicated chickenpox, and some children (exact number not reported) in the prednisolone arm in this RCT evidenced growth (height and weight) retardation at 1 year of age compared with children in the methylprednisolone arm (p values $\leq$0.003). Children (>70%) in both arms in this study also experienced blood pressures $\geq$ the 90th percentile (>15% in either arm were $\geq$ the 95th percentile) though only one required antihypertensive medication for persistent elevation, and 52 of 73 cortisol tests were abnormal (31 in prednisolone arm and 21 in methylprednisolone). Twelve cortisol levels in the prednisolone arm and one in the methylprednisolone arm were in the undetectable range, and blood glucose was transiently elevated in 5 of 70 tests.[85]

Table 8. Harms/adverse effects in comparative studies of steroids to treat IH

Harm/Adverse Event	N Studies Reporting Harm (# Participants With Harm/Total Participants)	Reported Rates Across Studies
Prednisolone 2mg/kg/day		
Irritability[85]	1 (3/10)	30%
Crying[85]	1 (3/10)	30%
Insomnia[85]	1 (3/10)	30%
Hyperactivity[85]	1 (2/10)	20%
Vomiting[85]	1 (2/10)	20%
Abdominal pain[85]	1 (2/10)	20%
Spontaneous ulceration[86]	1 (4/25)	16%
Persistent high blood pressure[85]	1 (1/10)	10%
Respiratory distress[85]	1 (1/10)	10%
Chickenpox[85]	1 (1/10)	10%
Prednisone 2.8 mg/kg/day		
Irritability[75]	1 (2/12)	17%
Oral thrush[75]	1 (2/12)	17%
Insomnia[75]	1 (1/12)	8%
Hypertension[75]	1 (1/12)	8%
Growth failure[75]	1 (1/12)	8%
IV methylprednisolone 30mg/kg		
Irritability[85]	1 (3/10)	30%
Crying[85]	1 (2/10)	20%
Hyperactivity[85]	1 (2/10)	20%
Vomiting[85]	1 (2/10)	20%
Abdominal pain[85]	1 (2/10)	20%
Insomnia[85]	1 (1/10)	10%
Apathy[85]	1 (1/10)	10%

Harm/Adverse Event	N Studies Reporting Harm (# Participants With Harm/Total Participants)	Reported Rates Across Studies
Behavioral change[85]	1 (1/10)	10%
Respiratory distress[85]	1 (1/10)	10%
Intralesional triamcinolone 1-5 mg/kg		
Pain[101]	1 (47/47)	100%
Itching[101]	1 (9/47)	19.1%
Bleeding[101]	1 (8/47)	17%
Infection[101]	1 (8/47)	17%
Spontaneous ulceration[86]	1 (1/25)	4%
Ulcer and depigmentation[86]	1 (1/25)	4%
Cushingoid appearance[101]	1 (1/47)	2.1%
Skin atrophy[86, 101]	2 (5/72)	4%-8.5%
Skin depigmentation or hypopigmentation[86, 101]	2 (6/72)	6.4%-12%
Oral corticosteroids (undefined)		
Cushingoid appearance	1 (42/42)	100%
Gastroesophageal reflux	1 (4/42)	10%
Arterial bleed	1 (4/42)	10%
Hirsutism	1 (4/42)	10%
Growth retardation	1 (4/42)	10%
Hypercholesterolemia	1 (4/42)	10%
Scarring and lip contraction	1 (4/42)	10%
Hypertension	1 (2/42)	5%
Mometasone furoate (topical)		
Itching[101]	1 (10/52)	19.2%
Hypopigmentation[101]	1 (4/52)	7.7%
Observation		
Spontaneous ulceration[86]	1 (4/25)	16%

Note: One study[33] comparing prednisolone and methylprednisolone regimens reported Cushingoid facies in 20/45 children, irritability in 16/45, and increased appetite in "almost all" children. The study does not report the regimen associated with each adverse event.
Abbreviations: IH = infantile hemangioma; n = number

Case series included 3155 children receiving intralesional, oral, or topical steroids or combinations of agents, with doses of oral steroids ranging from 1 to 5 mg/kg/day and intralesional doses (where reported) ranged from 0.5 to 6 ml (Table 9). We considered all studies as poor quality for harms reporting. No studies explicitly reported harms sought, and the lack of a comparison group and typically small sample sizes limit our understanding of the significance of these harms.

Frequently reported harms across agents were Cushingoid facies (reported in 0.45%-100% of children in 11 studies), diminished height or weight gain or growth retardation (0.45%-42% of children in seven studies), skin atrophy (0.95%-17% of children in five studies), hypopigmentation (1.4% to 16% of children in five studies), hypertension (0.11% to 5% of children in five studies), infection (2% to 15% of children in four studies), and behavioral changes (25% to 100% of children in four studies). Cushingoid appearance and growth retardation occurred regardless of dosage form (i.e., intralesional, oral).

Table 9. Adverse effects in case series of steroids to treat IH

Harm/Adverse Event	Number Of Studies (# Participants With Harm/Total Participants)	Reported Rates Across Studies
Intralesional triamcinolone+betamethasone		
Cushingoid appearance[88, 90]	2 (5/100)	3%-10%
Hypopigmentation[88]	1 (2/70)	3%
Periocular calcification[100]	1 (1/34)	3%
Intralesional triamcinolone+dexamethasone		
Abscess at injection site[89]	1 (1/27)	4%
Subcutaneous fat atrophy[89]	1 (1/27)	4%
Intralesional triamcinolone+prednisolone		
Ulceration[99]	1 (130/628)	21%
Skin atrophy[99]	1 (106/628)	17%
Hypopigmentation[99]	1 (101/628)	16%
Infection[99]	1 (91/628)	14%
Cushingoid appearance[99]	1 (37/628)	6%
Growth retardation[99]	1 (37/628)	6%
Hypertension[99]	1 (30/628)	5%
Intralesional triamcinolone		
Ulceration[92, 99]	2 (150/1046)	4%-16%
Infection[87, 99]	2 (105/991)	2%-12%
Anaphylactic shock[94]	1 (3/155)	2%
Hypopigmentation[92, 99]	2 (93/1046)	1%-10%
Peptic ulcer[92]	1 (2/160)	1%
*Skin atrophy[87, 94, 99]	3 (106/1146)	0.95%-11%
Entropion[92]	1 (1/160)	0.63%
Cushingoid appearance[94, 99]	2 (6/1041)	0.45%-1%
Growth retardation[99]	1 (4/886)	0.45%
Hypertension[99]	1 (1/886)	0.11%
Prednisone or prednisolone		
Cushingoid appearance[95]	1 (44/62)	71%
Diminished weight gain[95]	1 (26/62)	42%
Diminished height gain[95]	1 (22/62)	35%
Irritable and/or napped less[95]	1 (18/62)	29%
Personality change[95]	1 (18/62)	29%
Gastric irritation[95]	1 (13/62)	21%
Insomnia[95]	1 (8/62)	13%
Fungal (oral or perineal) infection[95]	1 (4/62)	6%
Recurrent otitis media[95]	1 (4/62)	6%
Corticosteroid myopathy[95]	1 (1/62)	2%
Hypertension[95]	1 (1/62)	2%
Prednisolone		
Cushingoid appearance[91, 99]	2 (26/524)	4%-20%
Infection[99]	1 (55/499)	11%
Growth retardation[99]	1 (21/499)	4%
Hypertension[99]	1 (20/499)	4%
Skin atrophy[99]	1 (16/499)	3%
Ulceration[99]	1 (13/499)	3%
Hypopigmentation[99]	1 (7/499)	1%
Prednisone		
Cushingoid appearance[93, 96]	2 (70/98)	53%-100%
Behavior changes[93, 96]	2 (66/98)	25%-100%
Growth retardation[93, 96]	2 (5/98)	3%-8%
Hypertension[93]	1 (2/38)	5%
Glucosuria[93]	1 (1/38)	3%
Osteoporosis[96]	1 (1/60)	2%

*One study[87] reported "atrophy and ulceration."
Abbreviations: IH = infantile hemangioma; n = number

Harms Reported in Package Insert Data

The safety and efficacy of pediatric use of corticosteroids has been studied in the literature for the treatment of nephrotic syndrome (>2 years of age), and aggressive lymphomas and leukemias (>1 month of age).[102-107] It has been reported that the adverse events identified in pediatric patients were similar to the events experienced in adults. Monitoring pediatric patients for blood pressure, weight, height, intraocular pressure, and clinical evaluation for the presence of infection, psychosocial disturbances, thromboembolism, peptic ulcers, cataracts, and osteoporosis is recommended. Specifically, pediatric patients may have a decrease in growth velocity after taking corticosteroids by any route of administration. Therefore, children should be titrated to the lowest effective dose.

Common adverse events of corticosteroids include: fluid retention, alteration in glucose tolerance, elevation in blood pressure, behavioral and mood changes, increased appetite and weight gain.[102-110] Additional adverse events include: anaphylactoid reaction, anaphylaxis, angioedema, bradycardia, cardiac arrest, cardiac arrhythmias, cardiac enlargement, circulatory collapse, congestive heart failure, fat embolism, hypertension, hypertrophic cardiomyopathy in premature infants, myocardial rupture following recent myocardial infarction, pulmonary edema, syncope, tachycardia, thromboembolism, thrombophlebitis, vasculitis, acne, allergic dermatitis, cutaneous and subcutaneous atrophy, dry scalp, edema, facial erythema, hyper or hypopigmentation, impaired wound healing, increased sweating, petechiae and ecchymoses, rash, sterile abscess, striae, suppressed reactions to skin tests, thin fragile skin, thinning scalp hair, urticaria, abnormal fat deposits, decreased carbohydrate tolerance, development of Cushingoid state, hirsutism, manifestations of latent diabetes mellitus and increased requirements for insulin or oral hypoglycemic agents in diabetics, menstrual irregularities, moon faces, secondary adrenocortical and pituitary unresponsiveness (particularly in times of stress, as in trauma, surgery or illness), suppression of growth in children, potassium loss, hypokalemic alkalosis, sodium retention, abdominal distention, elevation in serum liver enzymes levels (usually reversible upon discontinuation), hepatomegaly, hiccups, malaise, nausea, pancreatitis, peptic ulcer with possible perforation and hemorrhage, ulcerative esophagitis, osteonecrosis of femoral and humeral heads, Charcot-like arthropathy, loss of muscle mass, muscle weakness, osteoporosis, pathologic fracture of long bones, steroid myopathy, tendon rupture, vertebral compression fractures, arachnoiditis, convulsions, depression, emotional instability, euphoria, headache, increased intracranial pressure with papilledema (pseudo-tumor cerebri) usually following discontinuation of treatment, insomnia, meningitis, mood swings, neuritis, neuropathy, paraparesis/paraplegia, paresthesia, personality changes, sensory disturbances, vertigo, exophthalmos, glaucoma, increased intraocular pressure, posterior subcapsular cataracts, alteration in motility and number of spermatozoa.

We also identified safety data for another steroid evaluated in studies in this review, mometasone furoate. The use of this medication in pediatric patients (≥2 years) is not recommended for more than 3 weeks.[111] This medication is administered topically, and pediatric patients will have an increase in the skin surface area to body mass ratio. As a result, adverse events such as hypothalamic-pituitary-adrenal axis suppression, Cushing's syndrome, adrenal insufficiency upon cessation, skin atrophy, striae, linear growth retardation, delayed weight gain, and intracranial hypertension are more likely to occur in pediatric patients. We report additional

harms data form package inserts and U.S. Food and Drug Administration (FDA) approval documents in Appendix H.

Effectiveness and Harms of Beta-Blockers

Key Points

Propranolol vs. Observation or Placebo

- In our network meta-analysis, oral propranolol was associated with a mean estimate of expected clearance of IH of 95% (95% BCI: 86% to 100%) compared with 2 percent (95% BCI: 0% to 5%) for placebo or observation arms (high SOE for greater effectiveness of propranolol vs. placebo or observation).
- Oral propranolol at doses of 2-3 mg/kg/day divided two to three times daily and given for up to 6 months promoted resolution or near resolution of IH in children under the age of 12 months with superficial, deep, mixed, or ulcerated IH in most studies.
- Adverse events, measured in the short-term only, associated with these doses of propranolol in this same population were limited in frequency and severity (moderate SOE association of propranolol with clinically important and minor harms).

Propranolol vs. Other Active Modalities

- In network meta-analysis, oral propranolol was associated with a mean estimate of expected clearance of IH of 95% (95% BCI: 86% to 100%) compared with a lower rate for oral steroids (25% (95% BCI: 9% to 50%), while in head-to-head comparisons two small studies found propranolol was more effective than corticosteroids, and two did not find a significant difference in effectiveness between the two therapies. Combined effects from individual studies and meta-analysis conferred moderate SOE for the superiority of propranolol over steroids at achieving IH clearance.
- Propranolol combined with pulsed dye laser (PDL), either concurrently or sequentially, was more effective than propranolol alone in one study.
- In a study comparing oral propranolol with intralesional bleomycin, 6 children in each arm had at least 75 percent clearance of IH.
- One study found that patients who received propranolol had a lower likelihood of subsequent laser treatment than those who received other interventions.
- Propranolol was associated with faster healing of ulceration vs. historical treatments including laser and antibiotics.

Oral Propranolol vs. Other Beta-Blockers or Dosage Forms

- Other oral beta-blockers (atenolol, nadolol) investigated in three studies were reported to be effective in promoting IH resolution and potentially associated with fewer adverse events than propranolol (low SOE for an equivalent response of IH to propranolol, nadolol, or atenolol).

Timolol vs. Placebo/Observation or Other Active Modalities

- In our network meta-analysis, topical timolol had a mean expected clearance rate of 64 percent (95% BCI: 31% to 90%) compared with 2 percent (95% BCI: 0% to 5%) for placebo or observation (low SOE for effectiveness of timolol vs. placebo or observation).

- Topical timolol 0.5 percent maleate gel promoted improvement of superficial IH without reported adverse effects in four comparative studies (low SOE for lack of association with harms). Studies reported effectiveness at 24 weeks with the noticeable change in IH lesions occurring approximately 12 to 16 weeks after initiation of treatment.

Overview of the Literature

We identified a total of 57 studies (six RCTs,[13, 71, 72, 78, 80, 83] 13 cohort studies,[74-77, 79, 81, 82, 84, 112-117] and 38 case series[12, 14, 118-154]) addressing beta-blockers including propranolol, atenolol, nadolol, and timolol. Comparative studies addressed the following interventions and comparators: propranolol compared with observation or placebo arms, propranolol compared with other active modalities (e.g., steroids), oral propranolol compared with other beta-blockers or dosage forms, and timolol compared with observation/placebo or another modality. Comparative studies included a total of 1230 children between the ages of less than one month to 9 years. We considered four RCTs to be good quality and two as fair quality for effectiveness outcomes and 10 cohort studies as fair quality and three as poor quality for effectiveness outcomes.

Propranolol versus Observation or Placebo. We identified three studies (two good quality RCTs[13, 71] and one fair quality cohort study[73]) evaluating propranolol versus placebo or observation. Propranolol was associated with significantly greater clearance of IH compared with the control arm in all three studies. In the largest RCT, which included 456 children without problematic IH receiving 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.[71] 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 relative to 2 percent for placebo/observation arms; IH size reductions were greater in propranolol arms vs. 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. Eight studies compared propranolol to another modality including steroids, pulse dye laser (PDL), bleomycin, or historical treatments.[74-78, 112, 116, 117] Studies comparing propranolol and steroids had conflicting findings. Propranolol was more effective than steroids in two studies,[75, 76] while two others studies did not find effectiveness differed significantly between these treatments.[77, 78] One retrospective study found that PDL therapy either in conjunction with or subsequent to propranolol therapy is more effective than propranolol alone.[117] Another study found the likelihood of laser treatment was lower in participants treated with propranolol than participants who did not receive the medication.[116] The study that compared propranolol with bleomycin[74] 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.[112]

In head-to-head comparisons, propranolol was more effective than steroids in two studies; two other studies reported no significant difference between propranolol and steroids. In network meta-analysis, pulling data from multiple studies, propranolol was superior to oral steroids (95% clearance versus 29% clearance). These combined effects from individual studies and meta-analysis conferred moderate SOE for superiority of propranolol over steroids at achieving clearance.

Oral Propranolol vs. Other Beta-Blockers or Dosage Forms. Three small studies compared propranolol with nadolol[79] or atenolol,[80, 113, 114] and one study evaluated oral, intralesional, and topical propranolol.[72] Atenolol and nadolol demonstrated promising effects on lesion size (largely equivalent effectiveness of propranolol and atenolol and greater effectiveness 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 (n=11/15, 8/15, 5/15, respectively), but the difference among groups was not significant.[72]

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

Timolol vs. Placebo/Observation or Other Active Modality. Four studies addressed timolol (one RCT[83] and three cohort studies[81, 82, 84]). Timolol was significantly more effective than observation or placebo in three studies,[81-83] and one study comparing imiquimod with timolol did not demonstrate that one intervention was more effective than the other.[84] No harms of timolol were observed in any study. Timolol was more effective than placebo or observation in three comparative studies. In network meta-analysis, the mean expected clearance rate for topical timolol was 64 percent relative to 2 percent for placebo or observation arms. We considered SOE as low for the effectiveness of timolol compared with placebo or observation.

Harms of Beta-Blockers. In addition to these comparative studies, a total of 38 case series addressed beta-blockers for IH.[12, 14, 118-154] Of these, 11 were prospective observations,[12, 118-125, 127] and 27 were retrospective.[14, 115, 128-154]We assessed four case series as good quality for harms reporting,[135, 138, 148, 153] one as fair quality,[149] and 33 as poor quality.[12, 14, 118-134, 136, 137, 139-147, 150-152, 154] Eighteen comparative studies also reported harms data, and we assessed four as good quality for harms reporting[71, 78, 83, 84] and the remained as poor quality for harms reporting.[13, 72-77, 79-82, 112-114, 117] 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. Rates of significant clinically important harms ranged from 0 to 100 percent across studies of propranolol and from 1 percent to 50 percent for minor harms. We considered SOE as moderate for the association of propranolol with these harms. Data were insufficient to comment on harms in studies of nadolol and atenolol. No harms were observed in four small studies of timolol. We considered SOE to be low for lack of association of timolol with harms.

Detailed Analysis

Propranolol versus Placebo or Observation

One good quality RCT conducted in 56 centers in 16 countries randomized 460 infants from 35 to 150 days of age with a proliferating IH measuring at least 1.5 cm in diameter to treatment with either placebo twice daily for 6 months (n=55) or one of four oral propranolol treatment regimens (1 mg/kg/day of propranolol divided twice daily for 3 months (n= 99) or 6 months (n= 103); 3 mg/kg/day of propranolol divided twice daily for 3 months (n= 101) or 6 months (n= 102).[71] Patients were stratified by age group (35 to 90 days versus 91 to 150 days) and location of hemangioma (facial versus non-facial). The trial was a double-blind, phase 2 to 3 study with a two-stage adaptive design with selection of the propranolol regimen (dose and duration) at the end of stage 1 and further evaluation of the selected regimen in stage 2. Two independent, trained, validated readers centrally assessed digital photographs taken at each patient's 15 study visits for complete or nearly complete resolution, hemangioma evolution, and change in hemangioma size and color. Investigators at each site performed these same assessments, and assessed complications, adverse events, and use of other treatment for IH. Parents or guardians also assessed changes in IH since the previous visit.

The primary outcome, based on centralized evaluation of digital photographs, was complete/ near complete resolution or failure of treatment at week 24 versus baseline. In total, 323 of the 456 patients who received treatment completed 24 weeks of trial treatment and 343 completed follow-up to week 96. Patients were similar across treatment groups at baseline. Overall, 61 of 101 patients (60%) assigned to propranolol 3mg/kg/day for 6 months and 2 of 55 patients (4%) assigned to placebo had complete or near complete resolution of hemangioma at week 24 ($p<0.001$). This propranolol regimen remained superior to placebo when adjusting for age group, hemangioma location, and randomization ratio. However, only 40 percent of the cases judged centrally as "complete resolution" and "complete or nearly complete resolution" were assessed similarly by the on-site investigators. The on-site investigators noted sustained improvement from week 5 through week 24 in 71 percent of cases, which was similar to the rate determined by the centralized assessments.

The most frequent reason for discontinuation was treatment inefficacy. Of the 133 patients (29%) who discontinued treatment, 36 were receiving the 6-month placebo regimen, 35 were receiving the 3-month 1 mg/kg/day propranolol regimen, and 35 were receiving the 3-month 3 mg/kg/day regimen. Those with the lowest rates of discontinuation were patients receiving propranolol for 6 months at the 1 mg/kg/day dosing (n=14) and 3 mg/kg/day dosing (n= 13) regimens. Six (10%) patients assigned to the selected propranolol regimen required reintroduction of treatment from week 24 to week 96.

Another good quality RCT conducted in Australia randomized 40 children at a single center between the ages of 9 weeks and 5 years with IH that did not require urgent treatment to receive propranolol at 2 mg/kg/day divided three times daily or placebo for 6 months.[13] Patients were randomized within the strata of <6 months of age, >6 months of age, focal or segmental morphology. Nineteen patients were treated with propranolol, and IH growth stopped before week 4 of propranolol treatment in all patients. The largest difference in mean percent change in volume between the propranolol and placebo groups (based on serial hemispheric measurements of tumor volume) occurred at week 12 (-66.4%, $p = 0.03$). IH redness and elevation improved significantly more at weeks 12 and 24 in the propranolol compared to placebo group (p values ≤

0.07). Of the 19 patients treated with propranolol, two responded only minimally (start of treatment at ages 5.5 and 11 months).

In one fair quality cohort study conducted in India, thirty-three children up to 10 years of age with IH requiring treatment due to airway obstruction, ocular occlusion or compression, aesthetic disfigurement or ulceration, who may have failed other treatment modalities, and those patients greater than 12 months of age with continuous proliferation of their IH without signs of resolution were treated with propranolol at a dose of 2mg/kg/day divided twice daily.[73] The study compared these participants with historical controls who had not previously received therapy and had photographs available for assessment. Propranolol was administered until 1 year of age in patients ages 6 months or less. Patients older than 6 months received propranolol for 24 weeks. Those with partial response were administered an additional 12 weeks of therapy, and all participants were followed for 6 months following cessation of therapy. Outcome measures for both groups, assessed by five blinded investigators, included color and size of the IH, based on front and lateral photographs taken at weeks 1, 2, 3, 4, 6, and 8 then every 4 weeks thereafter. Significant involution defined as a score of 5 to 9 on a 10-point scale (10=no change in original IH, 0=normal skin) was seen in 28/31 (90.3%). All children 6 months of age and younger responded (20/20, 100%). No child greater than 36 months of age (0/2, 0%) responded to propranolol. Sixty-five to 80 percent of involution occurred in the first 8 weeks of propranolol therapy. The overall mean involution score for the propranolol group compared with the control group was 4.37 versus 8.38 ($p < 0.0001$). Table 10 outlines resolution outcomes in these studies.

Table 10. Key resolution outcomes in RCTs comparing propranolol and placebo or observation

Author, Year Comparison Groups (n) Quality	Age Type	Location	Methods and Measures of Resolution/ Response	Resolution Outcomes	Rebound Growth/ Recurrence, n (%) Other Outcomes
Leaute-Labreze et al. 2015[71] G1: Propranolol, oral 3mg/kg/day for 6 months (102) G2: Propranolol, oral 3mg/kg/day for 3 months (101) G3: Propranolol, oral 1mg/kg/day for 6 months (103) G4: Propranolol, oral 1mg/kg/day for 3 months (99) G5: placebo (55) **Quality:** Good	**Age, days mean±SD** G1: 101.6 ± 31.0 G2: 107.5 ± 30.1 G3: 102.6 ± 30.1 G4: 103.6 ± 33.1 G5: 103.9 ± 31.1 **Type, n (%)** Segmental G1: 5 (5) G2: 7 (7) G3: 7 (7) G4: 4 (4) G5: 2 (4) Localized G1: 91 (90) G2: 88 (88) G3: 90 (88) G4: 89 (91) G5: 48 (87) Indeterminate G1: 5 (5) G2: 5 (5) G3: 5 (5) G4: 5 (5) G5: 5 (9)	G1+G2+G3+G4+G5: Multiple	• Serial photographs and clinical assessment • Nearly complete resolution defined as minimal degree of telangiectasis, erythema, skin thickening, soft-tissue swelling, and distortion of anatomic landmarks	**Complete or nearly complete resolution at 24 weeks, n (%)** G1: 61/101 (60%) G5: 2/25 (4%) p< 0.0001	**Need for additional treatment** • 6 (10%) assigned to propranolol required systemic treatment from week 24 to week 96 • 7 (11%) required any additional hemangioma treatment
Hogeling et al. 2011[13] G1: Propranolol oral, 2mg/kg/day in 3 daily doses (19) G2: Placebo (20) **Quality:** Good	**Mean weeks, n** G1: 67 G2: 71 **Type** Focal, n G1: 16 G2: 17 Segmental G1: 3 G2: 3	**G1+G2:** multiple	• Photographs and serial hemispheric measurements of tumor volume	**Percent change in volume at 24 weeks** G1: -60% (n=18) G2: -14.1% (n=15) Difference between group -45.9 (95% CI: -80.3, -11.4) p=0.01	• NR

Author, Year Comparison Groups (n) Quality	Age Type	Location	Methods and Measures of Resolution/ Response	Resolution Outcomes	Rebound Growth/ Recurrence, n (%) Other Outcomes
Sondhi et al. 2013[73] G1: Propranolol oral, 2mg/kg/day (31) G2: No treatment, historical controls (14) **Quality:** Fair	**Age, mean months (range)** G1: 10.8 (1 mo-9 years) G2: 8.6 (3-20 mo) **Type, n:** Superficial G1: 11 G2: 6 Mixed G1: 9 G2: 3 Deep G1: 11 G2: 5	G1+G2: multiple	• Photographs, color and size scored; degree of involution • Change score: 0 considered completely normal skin, 10 no change in IH from pre-treatment	**Involution** Significant involution (> 50%), n (%) G1: 28 (90.3) G2: 4 (28.6) Some involution (11%- 50%), n (%) G1: 0 G2: 2 (14.3) No involution (≤ 10%), n (%) G1: 3 (9.7) G2: 6 (42.8) **Overall mean score** G1: 4.37 (95% CI: 3.15 to 5.59) G2: 8.38 (95% CI: 7.71 to 9.01) G1 vs.G2 p <0.0001	**Rebound growth** •No rebound growth in G1 6 months follow up after cessation of propranolol **Predictors of response** •100% of children ≤6 months old had complete response vs. 89% of children between 6 -36 months old, and 0 children older than 36 months •Greater magnitude of involution in children ≤6 months old •Greater decline in heart rate after treatment initiation in responders vs. non-responders (p-.0006

Abbreviations: CI = confidence interval; G = group; n = number; NR = not reported; RCT = randomized, controlled trial

Propranolol versus Other Active Modalities

Oral Propranolol versus Oral Steroids

Three studies compared oral propranolol with oral steroids (Table 11). A good quality RCT compared prednisolone (2 mg/kg/day) with propranolol (2 mg/kg/day) in 19 infants. [78] A blinded investigator evaluated the IH (or largest lesion if multiple IH were present) for type, ulceration, area, and degree of normal intervening skin. Participants were evaluated for four months after treatment, and an additional analysis used data from five month followup was used for participants who missed their four month appointment. The mean age of participants was 2.5 months in the propranolol group and 4.0 months in the steroid group. The mean duration of treatment was 4.0 months in the prednisolone group and 2.5 months in the propranolol group. Lesions were superficial (25%), deep (25%), and mixed (50%). The mean change in total surface area did not differ significantly between prednisolone and prednisone (0.41 vs 0.64 mm^2, p=0.12). The rate of total surface area decline was faster in the prednisolone group, and this discrepancy persisted when baseline lesion characteristics were taken into account. Three patients (2 in propranolol group, 1 in prednisolone group) had IH regrowth after medication weaning. This trial was halted early due to withdrawal of 75% (6/8) of the participants in the prednisolone group.

A fair quality retrospective cohort study compared 12 patients treated with propranolol (mean dose 2.7 mg/kg/day, range 2.5-3.5) matched with 12 historical patients treated with prednisone (mean dose 2.8 mg/kg/day, range 2.0-4.0).[75] Two nurses evaluated lesion color and size and rated percentage of improvement as stable or worse (0% improvement), slight improvement (<25%), moderate (25%-50%), good (50%-75%), or excellent (>75%) at one, two, and six months after treatment. At the six-month timepoint, a 100-mm visual analog scale was used with -100 as doubling in size, 0 as no change, and 100 as complete resolution. The mean age of participants at treatment initiation was similar (3.7 months for propranolol group vs 3.8 months for prednisone group), and lesions were superficial (17%), deep (33%), and mixed (50%). The mean duration of treatment was 3.7 months in the propranolol group and 3.8 months in the prednisone group. At all timepoints, propranolol was rated as more effective than prednisone (p=0.007 at 1 month, p=0.002 at 2 months, and p<0.001 at 6 months). Mean improvement using the VAS was 78.7 percent with propranolol versus 44.8 percent with prednisone (p<0.001).

A fair quality retrospective cohort study compared propranolol (target dose 2 mg/kg/day) with an unspecified oral corticosteroid (dose ranged from 2-4 mg/kg/day, most took 4 mg/kg/day).[76] There were 75 infants in the propranolol group and 42 in the corticosteroid group. The percentage of clearance was calculated from serial photographs and clinical examinations using lesion length, height, and width to calculate volume. Mean age of participants was similar (4.9 months in propranolol group and 4.5 months in corticosteroid group). The mean duration of treatment was 7.9 months in the propranolol group and 5.2 months in the corticosteroid group. Duration of followup was not reported. Overall, more patients in the propranolol group (56/68, 82%) than the corticosteroid group (12/42, 29%) achieved clearance of 75 percent or more (p<01). Some of the patients in the propranolol group had received corticosteroids prior to propranolol treatment. There was no significant difference in the proportion of propranolol-participants with at least 75 percent clearance when subanalyzed according to previous corticosteroid use.

Table 11. Resolution outcomes in studies comparing beta-blockers and steroids

Author, Year **Comparison Groups (n)** **Quality**	**Age, Months** **Type**	**Location**	**Methods and Measures of Resolution/ Response**	**Resolution Outcomes**	**Rebound Growth/ Recurrence, n**
Baumann et al. 2014[78] G1: Propranolol, 2mg/kg/day in 3 daily doses (11) G2: Prednisolone, 2mg/kg/day in two daily doses (8) **Quality:** Good	**Age, mean (95% CI)** G1: 2.5 (1.7-3.4) G2: 4.0 (2.8-5.2 **Type, n:** Superficial G1: 3 G2: 2 Mixed G1: 6 G2: 4 Deep G1: 2 G2: 2	G1+G2: multiple	• Size measured by proportional change in total surface area (TSA)	**Change in size at 4-5 months, TSA mean (95% CI)** G1: 0.57 (0.34 to 0.80) n=9 G2: 0.63 (0.14 to 1.11) n=6 G1 vs. G2: p=ns	G1: 2 G2: 1

Author, Year Comparison Groups (n) Quality	Age, Months Type	Location	Methods and Measures of Resolution/ Response	Resolution Outcomes	Rebound Growth/ Recurrence, n
Bertrand et al. 2011[75] G1: Propranolol, oral 2.7 mg/kg/day (12) G2: Prednisone, oral 2.8 mg/kg/day (12) **Quality:** Fair	**Age, mean (range)** G1: 3.7 (1.5-8.7) G2: 3.8 (1-9) **Type, n:** Superficial G1+G2: 2 pairs Mixed G1+G2: 6 pairs Deep G1+G2: 4 pairs	G1+G2: multiple	• Photographs rated for percentage of improvement Stable or worse (0%) Slight improvement (<25%) Moderate (25-50%) Good (50-75%) Excellent (>75%) • Visual analog scale (VAS) used at 6 months (100 complete resolution, 0 no change, -100 doubling in size)	**Clinical improvement VAS, mean ± SD** G1: 78.73 ± 22.47 G1: 44.82 ± 12.21 G1 vs.G2 ICC=0.833 p< 0.001 Good to excellent response at 6 months, n G1: 12 Slight to moderate response G2: 9	NR
Price et al. 2011[76] G1: Propranolol, oral 2/mg/kg/day in two daily doses (68) G2: Corticosteroids, oral 2-4 mg/kg/day (42) **Quality:** Fair	**Age, mean** G1: 4.9 G2: 4.5 **Type** NR	G1+G2: multiple	• Degree of clearance achieved reported as either 1. ≥75% defined by correlating percentage of decrease in volume, cosmetically acceptable result by physician and/or parent and no need for further treatment or 2. <75% clearance	≥ 75% clearance G1: 56/68 (82%) G2: 12/42 (29%) G1 vs. G2: p< 0.01	**Relapse** G1: 2-6 (data not clearly reported) G2: NR

Abbreviations: CI = confidence interval; G = group; NR = not reported; NS = not significant; SD = standard deviation; TSA = total surface area; VAS = visual analog scale

Intralesional Propranolol versus Intralesional Triamcinolone

A fair quality prospective cohort study compared a single intralesional propranolol injection with a single intralesional triamcinolone injection in 22 infants with periocular capillary hemangioma (Table 12).[77] Hemangioma size was assessed by clinical examination and documented with photos. Treatment response was graded as excellent (complete resolution), good (≥ 50% reduction in hemangioma size), fair (< 50% reduction in hemangioma size), or poor (no response or worsening of hemangioma). Astigmatic error and degree of ptosis were also assessed. Evaluation continued for four months after treatment. The mean age of participants was 5.9 ± 2.7 months in the propranolol group and 6.1 ± 2.9 months in the steroid group. Among the 12 participants who received propranolol, the response was excellent for five (42%), good for three (25%), fair for two (17%), and poor for two (17%). Among the 10 participants who received triamcinolone, the response was excellent for four (40%), good for two (20%), fair for two (20%), and poor for two (20%). Seven participants (four in the propranolol group and three in the triamcinolone group) experienced rebound growth after responding to treatment. All of these participants received and responded to a second injection. There were statistically

significant reductions in astigmatic error and degree of ptosis in both groups, and the differences between the two treatment groups were not statistically significant.

Table 12. Resolution outcomes in studies comparing intralesional propranolol and triamcinolone

Author, Year Comparison Groups (n) Quality	Age, Months Type	Location	Methods and Measures of Resolution/ Response	Resolution Outcomes	Rebound Growth/ Recurrence Other Outcomes
Awadein et al. 2011[77] G1: Propranolol, intralesional 1mg/ml (12) G2: Triamcinolone, intralesional 40mg/ml(10) **Quality:** Poor	**Age, mean±SD** G1: 5.9±2.7 G2: 6.1±2.9 **Type** NR	G1+G2: Periocular	• Size measured by clinical examination and photography • Response graded as: Excellent-complete resolution achieved Good-sustained plateau with ≥ 50% reduction Fair-sustained plateau with < 50% reduction Poor-no response or worsening	**Regression of hemangioma** G1:10/12 (83%) G2: 8/10 (80%) **Response** Excellent response G1:5/12 (42%) G2: 4/10 (40%) Good G1:3/12 (25%) G2: 2/10 (20%) Fair G1:2/12 (17%) G2: 2/10 (20%) Poor G1:2/12 (17%) G2: 2/10 (20%)	**Rebound growth, n** G1:4 G2: 3 **Vision outcomes** •Significant reduction in astigmatic error in both the propranolol group (p=0.02) and the steroid group (p=0.03) but there was no between group differences (p=0.34, n=22) •No significant group difference in the degree of ptosis (p=0.46)

Abbreviations: G = group

Propranolol plus Pulsed Dye Laser versus Propranolol Alone

A fair quality retrospective cohort study compared three treatments for facial segmental IH: concurrent propranolol and pulsed dye laser (n=12), propranolol followed by pulsed dye laser (n=5), and propranolol alone (n=8) (Table 13).[117] Two blinded dermatologists evaluated the degree of hemangioma clearance in photos of participants. Clearance was rated as 1 (no improvement), 2 (partial improvement, significant residual superficial or deep IH), 3 (near-complete clearance, mild residual superficial IH), or 4 (complete clearance, minimal to no residual superficial IH). Mean age at treatment initiation ranged from 43 days in the concurrent propranolol and pulsed dye laser group to 47 days in the propranolol-only group to 62 days in the propranolol followed by pulsed dye laser group. Mean hemangioma size was larger in the concurrent treatment group (41.65 cm^2) than the sequential (20.1 cm^2) and propranolol-only groups (18.0 cm^2). Treatment duration ranged from 275.4 days in the propranolol followed by pulsed dye laser group to 276.2 days in the concurrent propranolol and pulsed dye laser group to 288.0 days in the propranolol-only group. Duration of followup was not reported. Among the 12 participants who received concurrent propranolol and pulsed dye laser, six (50%) had complete clearance and six (50%) had near-complete clearance. All five of the participants in the propranolol followed by pulsed dye laser group also had complete (n=2, 40%) or near-complete

(n=3, 60%) clearance. Among the eight participants who receive propranolol alone, one (13%) had complete clearance, two (25%) near-complete clearance, and five (63%) partial clearance. The difference in effectiveness between combined therapy, either concurrently or sequentially, and propranolol alone was statistically significant. The number of days of propranolol treatment until near-complete clearance was significantly lower (p <.001) for those receiving concurrent therapy (mean 92.3 ± 50.9 days) or sequential therapy combined therapy (mean 181.2 ± 101.1 days) than those receiving propranolol alone (mean 288.0 ± 83.5 days).

Table 13. Resolution outcomes in studies comparing propranolol with laser and propranolol alone

Author, Year **Comparison Groups (n)** **Quality**	**Age, Months** **Type**	**Location**	**Methods and Measures of Resolution/ Response**	**Resolution Outcomes**	**Rebound Growth/ Recurrence** **Other Outcomes**
Reddy et al. 2013[117] G1: Propranolol + pulsed dye laser concurrent (12) G2: Propranolol followed by pulsed dye laser (5) G3: Propranolol only (8) **Quality:** Fair	**Age, mean days** G1: 43 G2: 62 G3: 47 **Type, n (%)** Superficial G1: 7 (58) G2: 0 G3: 3 (37.5) Compound G1: 5 (42) G2: 5 (100) G3:5 (62.5)	G1+G2+G3: Large or segmental-distribution facial	• Photographs used to rate degree of clearance score: 1: no improvement 2: partial improvement (significant residual superficial or deep IH) 3: near-complete clearance (mild residual superficial IH) 4: complete clearance (minimal to no residual superficial IH)	**Complete clearance** G1: 6/12 (50) G2: 2/5 (40) G3: 1/8 (12.5) G1 vs.G2 vs.G3: p=0.01	**Rebound growth** NR **Other outcomes** • Significant difference between groups in the number of days of propranolol treatment until near-complete clearance of lesions, p<0.001 • Concurrent combination therapy group achieved near-complete clearance after fewest days of propranolol treatment; G2 after a longer period of treatment; and G3 after the longest period

Abbreviations: G = group; IH = infantile hemangioma; NR = not reported

Oral Propranolol versus Intralesional Bleomycin

A poor quality prospective cohort study compared oral propranolol with intralesional bleomycin in 20 children with cutaneous hemangioma (Table 14).[74] Participants either received daily oral propranolol for six weeks or three bleomycin injections given at 6-week intervals. Photos were used to assess treatment effectiveness which was graded from I to V based upon the percent reduction in size (I >90%, II 75% to 90%, III 50% to 75%, IV 25 to 50%, V <25%). Participants were followed for five months. Participants ranged in age from 6 months to 5 years; more than half of participants were infants (n not specified). In the bleomycin group (n=7 at final follow up), one participant had a grade I response, five a grade II response, and two a grade III response. In the propranolol group (n=10), two participants had a grade I response, four a grade II response, three a grade III response, and one a grade IV response. Children who received propranolol began responding to treatment more quickly than those who received bleomycin.

Table 14. Resolution outcomes in studies comparing propranolol and bleomycin

Author, Year Comparison Groups (n) Quality	Age, Months Type	Location	Methods and Measures of Resolution/ Response	Resolution Outcomes	Rebound Growth/ Recurrence Other Outcomes
Thayal et al. 2012[74] G1: Propranolol, oral 2 mg/kg/day (10) G2**:** Bleomycin, intralesional 0.5 mg/kg (10) **Quality:** Poor	**Age** NR **Type, %** Cutaneous: G1+G2:100	NR	Regression in size of lesion 5 grades: I Complete involution (> 90% response) II Reduction in size 75-90% III Reduction 50-75% IV Reduction 25-50% V Reduction < 25%	**Response, n** Grade I response G1: 2 G2: 1 Grade II response G1: 4 G2: 5 Grade III response G1: 3 G2: 2 Grade IV response G1: 1 G2: NR	NR

Abbreviations: G = group; n = number; NR = not reported

Propranolol versus No Propranolol

A fair quality retrospective cohort study examined the effect of propranolol on the incidence of invasive procedures in 58 children with nasal IH.[116] Two independent reviewers assigned lesions one of four grades depending on depth of the lesion, nasal subunit involvement, and functional impairment. Participants fell into three groups: treated in the pre-propranolol era (n=20), treated in the post-propranolol era and received propranolol (n=25), and treated in the post-propranolol era and did not receive propranolol (n=13). The mean age at treatment initiation was 4.9 months for both groups treated in the post-propranolol era and 4.1 months for the group treated in the pre-propranolol era. In the group that received propranolol, the mean duration of therapy was 7.6 months. Duration of followup was not reported. Many participants received other therapies including corticosteroids, laser treatments, and/or surgery. Participants who received propranolol had a lower likelihood of laser treatment than those treated in the pre-propranolol era (hazard ratio 0.44, 95% CI: 0.27 to 0.78). The risks of surgical excision did not differ significantly (hazard ratio 0.45, 95% CI: 0.15 to1.38).

Another fair quality cohort study conducted in the Netherlands compared 20 children with ulcerated IH treated with propranolol with 20 historical controls (matched on age at IH onset, extent of ulceration, and type, location and size of the IH).[112]Children in the control group had received steroids (25%), PDL (1%), antibiotics (60%), and local wound care (100%). Propranolol was administered at a starting dose of 0.7 to 1 mg/kg per day divided into three daily doses, increased over a 3-day period to 2 to 2.5 mg/kg/day, and continued until approximately 1 year of age. Blood pressure, heart rate, and fasting glucose levels were monitored the first 3 days of propranolol dosing. Anatomic locations and types of the ulcerating IH were primarily the head and neck region (70%), superficial nodular (70%), and localized (70%). Mean age of starting propranolol was 3.5 months of age and average treatment duration for 19 of the 20 patients who completed propranolol treatment was 9.1 months. Mean age of the patients at the start of ulceration was 2.3 months, and complete healing occurred after an average total ulceration time of 8.7 weeks in the propranolol treated group versus 22.4 weeks (p= 0.012) in the historical control group. Four of 19 (20%) patients who completed propranolol treatment had regrowth.

One (0.5%) patient restarted propranolol due to significant regrowth of the IH, affecting surrounding structures. Table 15 outlines key outcomes.

Table 15. Key outcomes in studies comparing propranolol and no propranolol

Author, Year Comparison Groups (n) Quality	Age, Months Type	Location	Key Outcomes, n
Perkins et al. 2014[116] G1: Propranolol era 2mg/kg/day, received (25) G2: Propranolol era, did not receive (13) G3: Pre-propranolol era (20) **Quality:** Fair	**Age**, **Mean (range)** G1: 4.9 (2.0- 13.5) G2: 4.9 (2.2-14.7) G3: 4.8 (2.0-14.3) **Type, %** Superficial and subcutaneous G1+G2+G3: 100	G1+G2: nasal	• 56% of G2 less likely to have any type of invasive treatment when compared to G1 (HR: 0.44, 95% CI: 0.27 to 0.73) • G2 and G3 were 35% less likely to have any type of invasive treatment (HR: 0.65, 95% CI: 0.42 to 1.00) when compared to G1 • 55% of G2 (HR: 0.45) less likely to have surgical excision and 56% (HR: 0.44, 95% CI: 0.27 to 0.78) less likely to have laser treatment when compared to G1 • G2 and G3 61% (HR:0.39) less likely to have surgical excision and 25% (HR: 0.75; 95% CI: 0.46 to 1.25) less likely to have laser treatment when compared to G1
Hermans et al. 2011[112] G1: Propranolol 2.0 to 2.5/mg/kg/d in three daily doses (20) G2: Historical controls (varied treatments) (20) **Quality:** Fair	**Age, mean at start of ulceration** G1: 2.3 G2: 2.7 **Type, n:** Superficial nodular G1: 14 Superficial macular G1: 4 Mixed G1: 2	G1+G2: multiple	• Complete healing from ulceration G1: 8.7 weeks G2: 22.4 weeks G1 vs.G2: p<0.015 • 4 (21.1%) of 19 children who completed treatment showed some regrowth and slightly increased redness after stopping propranolol but no recurrence of ulceration. 1 child (unclear if one of the 4 above) restarted due to regrowth

Abbreviations: CI = confidence interval; G = group; HR = hazard ratio; n = number

Oral Propranolol versus Other Beta-Blockers or Dosage Forms

Atenolol versus Propranolol

In a fair quality RCT conducted in Chile, investigators randomized 23 infants from 1 to 15 months of age with IH displaying functional impairment, aesthetic disfigurement, ulceration, or location on skin folds to receive oral atenolol (1 mg/kg/day in a daily dose) or oral propranolol (2 mg/kg/day divided into 3 daily doses) for 6 months.[80] Response, evaluated clinically and with photographs, was categorized as complete (complete resolution with or without telangiectasia and/or redundant tissue), partial (any size reduction or change not meeting complete response) or no response. Of 13 patients randomized to atenolol, seven had complete response (53.8%) compared with six of 10 children randomized to propranolol (60%) (p = 0.68). Upon cessation of treatment, four (40%) children in the propranolol group and two (15.4%) in the atenolol group had rebound growth.

In a fair quality cohort study conducted in the Netherlands, 30 consecutive infants ages 1.5 to 30 months (median age 6.4 months) with problematic IH were treated with atenolol (final dose of

1-3 mg/kg/day) compared with a historical control cohort of 28 infants with IH treated with propranolol (mean dose 2 mg/kg/day).[113, 114] The primary endpoint of change in IH appearance as evaluated by a 100-mm visual analogue scale (VAS, +100=complete resolution, -100=doubling in size/extent) and assessed by two blinded investigators using digital photographs comparing baseline and two time points after initiation of therapy: 2 to 8 weeks (t1) and 11 to 24 weeks (t2). Hemangioma Activity Score (HAS) was used to score the proliferative activity of the IH to assess therapeutic effect. Clinical assessment (color change, softening to palpation and reduction in size) was a secondary endpoint. Seven patients in total were excluded from quantitative assessment of efficacy; three patients treated with atenolol were excluded due to prior propranolol treatment or non-cutaneous IH and four patients treated with propranolol were excluded due to non-cutaneous IH location. Of the remaining 27 patients treated with atenolol and 24 patients treated with propranolol, those treated with atenolol were significantly younger than those treated with propranolol (p = 0.01). In addition, while not significant, the atenolol group contained more patients with ulceration (30% versus 4%).

There were no statistically significant differences noted in quantitative improvement of IH by VAS scores or change in HAS scores between the groups. Twenty-seven of 30 infants treated with atenolol (90%) and all patients treated with propranolol showed clinical involution at the end of the treatment period (p= 0.09). Table 16 outlines key outcomes.

Table 16. Resolution outcomes in studies comparing beta-blockers

Author, Year Comparison Groups (n) Quality	**Age, Months** **Type**	**Location**	**Methods and Measures of Resolution/ Response**	**Resolution Outcomes**	**Rebound Growth/ Recurrence, n (%)**
Abarrzua-Araya et al. 2014[80] G1: Propranolol, oral 2mg/kg/day in 3 daily doses for 6 months (10) G2: Atenolol, oral1mg/kg/day single daily dose for 6 months (13) **Quality:** Fair	**Age, mean±SD** G1+G2: 5.2±3.5 (range: 2-14) **Type, n:** Superficial G1+G2: 9 Mixed G1+G2: 13 Deep G1+G2: 3	**G1+G2:** multiple	• Serial photographs and clinical assessment • Complete response= complete resolution of IH • Telangiectasia and redundant tissue considered complete response • Partial response=any size reduction or change in color/consistency that did not meet complete response criteria • No response=no change in photographs and/or growth	**Response** Complete response G1: 6/10 (60%) G2: 7/13 (53.8%) G1 vs. G2: p=ns Partial response G1: 4/10 (40%) G2: 6/13 (46.1%) G1 vs. G2: p=ns **Response by Type** Superficial IH Complete response G1+G2: 5/9 (55.5) Mixed IH G1+G2: 3/13 (23) Deep IH G1+G2: 3/3 (100)	**Recurrence** G1+G2: 6 (26%) G1: 4/10 (40%) G2: 2/13 (15.4)

Author, Year Comparison Groups (n) Quality	Age, Months Type	Location	Methods and Measures of Resolution/ Response	Resolution Outcomes	Rebound Growth/ Recurrence, n (%)
De Graaf et al, 2013[113-115] G1: Atenolol, oral 1 mg/kg/day up to 3 mg/kg (30) G2: Propranolol, oral 2mg/kg/day (historical group) (28) **Quality:** Fair	**Age, n (%)** 1-6 months G1: 12/24 (50) G2: 23/27 (85) 6-12 months G1: 8/24 (33) G2: 4/27 (15) Over 12 months G1: 4/24 (17) G2: 0 **Type, n (%)** Localized/ nodular G1: 19/24 (79%) G2: 19/27 (70%) Segmental G1: 3/24 (13%) G2: 2/27 (8%) Indeterminate G1: 2/24 (8%) G2: 6/27 (22%) Multifocal G1: 0 G2: 0	G1+G2: multiple	• Serial photographs and clinical assessment of involution (color change, softening to palpation and reduction in size) • Visual analog scale (VAS) and hemangioma activity score (HAS)	**Clinical involution, n (%)** G1: 27 (90) G2: 28 (100) VAS and HAS scores shown in figures only G1 vs. G2 p= NS	NR

Abbreviations: G = group; HAS = hemangioma activity score; IH = infantile hemangioma; n = number; NR = not reported; NS = not significant; VAS = visual analog scale

Nadolol versus Propranolol

In a poor quality assessor-blinded cohort study conducted in Canada, oral nadolol was used in the six month treatment of 10 infants 1-month to 1-year of age and compared to a historical group of nine similar infants matched for age and hemangioma location who were treated with oral propranolol for at least six months (Table 17).[79] Infants were treated with oral nadolol starting at 0.5 mg/kg/day divided twice daily and increased weekly by 0.5 mg/kg to a maximum dose of 4 mg/kg/day (mean dose 2.19 ± 1.1 mg/kg). Propranolol was administered to a maximum of 2-3 mg/kg/day divided three times daily (mean dose 1.89 ± 0.29 mg/kg). Infants were evaluated at baseline by history, physical examination, vital signs, growth parameters, electrocardiogram, and digital photography. Follow-up visits included adverse event reviews and parental assessment of improvement. An investigator blinded to the intervention assessed percentage improvement of IH at 24 weeks using a 100-mm VAS. Correlation between assessor and parental assessment and frequency and severity of adverse events were secondary outcomes. There were no differences at baseline among the two groups. The nadolol treated group had a mean percentage IH shrinkage of 97 ± 3.05 percent at the 24-week visit compared with 86 ± 14.82 percent shrinkage observed in the propranolol group ($p < 0.001$).

Table 17. Key resolution outcomes in studies comparing nadolol and propranolol

Author, Year Comparison Groups (n) Quality	Age, months Type	Location	Methods and Measures of Resolution/Response	Resolution Outcomes	Rebound Growth/ Recurrence, n (%)
Pope et al, 2012[79] G1: Nadolol suspension up to 4 mg/kg/day (10) G2: Propranolol maximum dose 2-3 mg/kg/day (historical group) (9) **Quality:** Poor	**Age, mean±SD** G1: 4.1 ± 2.23 G2: 4.8 ± 1.92 **Type, n:** Superficial and deep G1: 6 G2: 9 Deep G1: 4 G2: 0	G1+G2: multiple	• Serial photographs and clinical assessment using 100-mm visual analog scale (VAS) (-): 100% worsening 0: no change (+): 100% shrinkage where 5 mm represented 10% change	**Percentage IH shrinkage, mean ± SD** G1: 97 ± 3.05% G2: 86 ± 14.82% G1 vs.G2: p< 0.008	NR

Abbreviations: G = groups; IH = infantile hemangioma; mm = millimeter; n = number; NR = not reported; SD = standard deviation

Oral Propranolol Compared with Other Dosage Forms

In a fair quality single blinded RCT conducted in Egypt, 45 consecutive patients with problematic, superficial IH (rapidly progressive, compromising vital or normal physiological function, or causing cosmetic disfigurement) were assigned to one of three treatments: oral propranolol (2 mg/kg/day divided into two daily doses, n=15), topical propranolol 1 percent ointment applied twice daily, or intralesional propranolol (1 mg propranolol hydrochloride as a 1 mL injection, n=15) repeated weekly (0.2 mL injected per 1 cm lesion diameter to a maximum of 1 mL, doses divided among multiple lesions, n=15) (Table 18).[72] Two investigators assessed photographs before and after therapy to determine response. Twelve (80%) patients treated with oral propranolol had improvement in their IH: nine (60%) patients showed a complete response; 2 (13.3%) demonstrated a sustained plateau with ≥ 50 percent reduction in size; 1 (6.7%) showed a sustained plateau with <50 percent reduction in size. Two children (13.3%) had no response to treatment and one (6.7%) discontinued treatment.

Ten (66.7%) patients treated with topical propranolol had improvement in their IH. Three (20%) demonstrated complete response; 5 (33.3%) demonstrated a sustained plateau with ≥ 50 percent reduction in size, 2 (13.3%) showed a sustained plateau with < 50 percent reduction in size, and five (33.3%) had no response to treatment. Eight (53.3%) patients treated with intralesional propranolol showed improvement in their IH. Two (13.3%) participants had a complete response; three (20%) demonstrated a sustained plateau with ≥ 50 percent reduction in size; three (20%) had a sustained plateau with < 50 percent reduction in size, seven children (46.7%) had no response. Rebound growth was documented in one (6.7%), one (6.7%) and two (13.3%) children treated with oral, topical, and intralesional propranolol, respectively. Time to achieve initial response and duration of treatment needed to achieve the final response were significantly greater in both the topical (3-8 weeks to initial response; 5-10 months treatment duration) and intralesional propranolol (4-8 weeks to initial response; 5-12 months treatment

duration) groups as compared with the oral propranolol group (2-4 weeks to initial response; 3-9 months treatment duration, p values ≤ 0.01).

Table 18. Resolution outcomes in studies comparing forms of propranolol

Author, Year Comparison Groups (n) Quality	Age, Months Type	Location	Methods and Measures of Resolution/Response	Resolution Outcomes	Rebound Growth/Recurrence, n (%)
Zaher et al. 2013[72] G1: Propranolol oral, 2mg/kg/day in 2 daily doses (15) G2: Propranolol, topical, 1% ointment applied twice daily (15) G3: Propranolol, intralesional, 1mg injected weekly (15) **Quality:** Fair	**Age, mean±SD (range)** G1+G2+G3: 8.82±4.6 (3-18) G1: 9.13 (3-18) G2: 8.33 (1-18) G3: 9.0 (3-18) **Type** NR	**G1+G2+ G3:** multiple	• Grading system comparing photographic documentation • Excellent: complete resolution achieved • Good: sustained plateau with ≥ 50% reduction in size • Fair: sustained plateau with < 50% reduction in size • Poor: no response or worsening of IH	**Response to treatment, n (%)** Excellent response G1: 9 (60) G2: 3 (20) G3: 2 (13.3) Good response G1: 2 (13.3) G2: 5 (33.3) G3: 3 (20) Fair G1: 1 (6.7) G2: 2 (13.3) G3: 3 (20) Poor G1: 3 (20) G2: 5 (33.3) G3: 7 (46.7)	**Rebound growth, n (%)** G1: 1 (6.7) G2: 1 (6.7) G3: 2 (13.3)

Abbreviations: G = group; IH = infantile hemangioma; n= number; SD = standard deviation

Timolol vs. Placebo/Observation or Other Modalities

Timolol Compared with Placebo or Observation

In a good quality double-blind, placebo-controlled, single institution RCT conducted in Australia, investigators randomly assigned 41 infants ages 5 to 24 weeks with small, focal, superficial IH not requiring systemic therapy to treatment with placebo (n=22) or timolol maleate 0.5 percent gel (n=19).[83] Response to therapy was measured by predicted absolute volume (0.07 x m^3; where m= the average of two hemispheric measurements of the lesion taken at 90 degrees apart) at weeks 1, 2, 3, 4, 8, 12, 16, 20 and 24 and by clinical photographs obtained at 1, 12, and 24 weeks and scored by a blinded investigator based on redness. Infants were not stratified by age or lesion size prior to randomization given the small number of participants.

Investigators reported a significant increase in the number of IH lesions decreasing in size by ≥5 percent in the timolol group compared with the placebo group at weeks 8 (37% vs. 5%, p= 0.04), 20 (47% vs.6%, p= 0.02), and 24 (60% vs.11%, p= 0.01). At 24 weeks, 47 percent of the timolol treated group had significantly increased difference in blinded photo score of 0 (no redness) compared with 6 percent in the placebo group, while the proportion of lesions completely red in the treatment group (6%) was significantly less than the placebo group (55%, p values <0.01).

In a fair quality trial conducted in the United States, children with non-vision-threatening IH (defined as absence of visually significant ptosis or induced astigmatism on initial examination)

were either observed (those presenting between August 1, 2007 and March 30, 2009) or offered treatment (presenting April 1, 2009 and January 15, 2011) with topical 0.25 percent timolol maleate gel.[81] The primary study outcome was response to treatment based on photographs (good response=decrease in size by more than 50 percent; moderate=stable or decrease by 50 percent or less; and poor=enlargement or visually significant ptosis or induced astigmatism at two months follow-up) and evaluated by a reviewer blinded to treatment or observation. Mean age at presentation was 4.8 months and 3.7 months for the treatment and observation groups respectively (p = 0.31). At 2 months follow-up, a good response was observed in eight (61.5%) infants, moderate response in four (30.8%) and one (7.7%) infant had a poor response in the treatment group compared with good response observed in no (0%) infants, a moderate response seen in one (10%) infant, and nine (10%) infants with poor response in the control arm. In addition, five (100%) superficial lesions and three (42.9%) mixed lesions treated with timolol demonstrated a good response, while four (57.1%) deep lesions treated with timolol demonstrated a moderate response. Overall, timolol-treated patients had significantly improved responses compared with the observation group (p=0.001). One patient in whom timolol was prematurely stopped at 5 months of age had rebound growth, which again regressed with resumption of topical timolol.

In a poor quality prospective cohort study conducted in China, 124 infants ≤ 12 months of age with superficial IH (≤ 3 mm in height) and without prior treatment or tumor regression were treated with either topical 0.5% timolol maleate drops three times daily (n=101) or observed (n= 23).[82] Patients were evaluated at 1 week and 4 months following initiation of timolol. Timolol promoted regression in 57 patients (56.4%), controlled growth in 36 patients (35.6%), and was ineffective in 8 patients (7.9%) compared with the observation group where regression was seen in one patient (4.3%), controlled growth observed in seven (30.4%), and continued growth observed in 15 patients (65.2%). Regression and efficacy rates in the timolol group compared to the observation group were significantly improved (p <0.05). At 3 to 5 months followup, no regrowth was noted in 12 patients followed who had complete regression of their IH. Table 19 outlines key outcomes.

Table 19. Key resolution outcomes in studies comparing timolol and observation or placebo

Author, Year Comparison Groups (n) Quality	Age, Months Type	Location	Methods and Measures of Resolution/ Response	Resolution Outcomes	Rebound Growth/ Recurrence, n (%)
Chan et al. 2013[83] G1: Timolol maleate 0.5% gel (19) G2: Placebo (22) **Quality:** Good	**Age, mean±SD** G1: 2.1 ± 0.8 G2: 3 ± 0.9 **Type, %:** Superficial G1+G2: 100	G1+G2: multiple	Serial photographs and clinical assessment volume estimation	**Infants with IH volume reduced by ≥ 5%, n (%)** G1: 15 (60) G2: 18 (11) G1 vs.G2: p=0.01 **Redness score** No redness, n (%) G1: 15 (47) G2: 18 (6) Half red, % G1: 47 G2: 39 Completely red, % G1: 6 G2: 5 G1 vs.G2 p= 0.003	No clinically significant rebound occurred in those successfully treated

Chambers et al. 2012[81] G1: Timolol maleate gel 0.25% (13) G2: Observation (10) **Quality:** Fair	**Age, mean±SD** G1: 4.8 G2: 3.7 **Type, n** Superficial G1: 5 G2: 4 Mixed G1: 7 G2: 5 Deep G1: 1 G2: 1	Periocular (100%)	Photographs Response categorized as good (lesion decreased by more than 50% size), moderate (lesion decreased by 50% or less) and poor (lesion enlarged or caused ptosis or induced astigmatism	**Response to treatment, n (%)** Good G1: 8 (61) G2: 0 Moderate G1: 4 (31) G2: 1 (10) Poor G1: 1 (8) G2: 9 (90) G1 vs.G2 p=0.001	NR
Yu et al. 2013[82] G1: Timolol , topical, drops three times daily(101) G2: Observation (23) **Quality:** Poor	**Age** 1-6 months G1+G2: 88 7-12 months G1 +G2: 36 **Type, %** Superficial: 100	G1+G2: multiple	Photographs Class 1: ineffective Class 2: controlled growth Class 3: promoted regression	**Response to treatment, n (%)** Class 1 G1: 8 (7.9) G2: 15 (65.2) Class 2 G1: 36 (35.6) G2: 7 (30.4) Class 3 G1: 57 (56.4) G2: 1 (4.3)	In 12 patients with complete resolution, no regrowth noted at 3-5 month followup

Abbreviations: G = group; IH = infantile hemangioma; n = number; SD = standard deviation

Imiquimod Cream versus Timolol Ophthalmic Solution

One fair quality retrospective cohort study evaluated imiquimod cream versus timolol ophthalmic solution for treatment of superficial proliferating IH (Table 20).[84] Two investigators compared baseline photos with images from the most recent visit. A 200-mm VAS was used to score the change in the hemangioma: -100 represented doubling in the size and extent of the IH, 0 represented no change, and +100 represents complete disappearance. The investigators also assessed the Hemangioma Activity Score (HAS) for the photos then calculated the change in the HAS between photos. There were 40 treated IHs among the participants: 24 on the head and neck, 8 on the trunk, and 8 on the limbs. The mean age of participants was 3.1 ± 1.20 months in the imiquimod group and 3.0 ± 1.96 months in the timolol group. The mean duration of therapy was 4.6 months in the imiquimod group and 4.3 months in the timolol group. Duration of followup was not reported. The VAS score and change in the HAS did not different significantly between the two groups.

Table 20. Resolution outcomes in studies comparing timolol and imiquimod

Author, Year Comparison Groups (n) Quality	Age, Months Type	Location	Methods and Measures of Resolution/Response	Resolution Outcomes, n	Rebound Growth/ Recurrence Other Outcomes
Qiu et al. 2013[84] G1: Imiquimod 5% cream (20) G2: Timolol ophthalmic 0.5% solution (20) **Quality:** Fair	**Age, mean±SD,** G1: 3.1 ± 1.20 G2: 3.0 ± 1.96 **Type, %** Proliferating superficial G1+G2: 100	G1+G2: multiple	• Visual analog scale (VAS) • Hemangioma Activity Score (HAS)	VAS and HAS results presented in figures VAS G1 vs.G2 p=0.11 Δ HAS G1 vs.G2 p=0.49	NR

Abbreviations: G = group; HAS = hemangioma activity score; n = number; NR = not reported; SD = standard deviation; VAS = visual analog scale

Harms of Beta-Blockers

Harms Reported in Studies Included in This Review

Twelve comparative studies specifically defined harms of beta-blockers used to treat IH.[13, 71-73, 78-81, 83, 84, 112, 114] Several studies specifically noted that no harms were observed: one study evaluating topical timolol maleate 0.5 percent gel compared to placebo;[83] a cohort study evaluating topical 0.25 percent timolol maleate gel;[81] one RCT of ophthalmic timolol,[84] and a cohort study of timolol that informed parents of potential adverse effects to monitor for, reported evaluating for safety (non-specified), and stated that no adverse effects were reported.[82] An RCT comparing atenolol versus propranolol[80] and two other cohort studies of intralesional propranolol[77] and up to 2mg/kg/day of oral propranolol[74] reported that no harms were observed.

One RCT comparing propranolol and prednisolone reported side effects associated with 2 mg/kg/day dosing of propranolol in the categories of allergy/immunology (0.02% of lesions), dermatologic (0.05% of lesions), gastrointestinal (0.11% of lesions), infection (0.11% of lesions), pulmonary/respiratory (0.32% of lesions), vascular (0.07% of lesions).[78]Fewer severe adverse events occurred in the propranolol arm compared with prednisolone (1 vs. 11, p=0.01); the one severe event in the propranolol arm was a case of dehydration necessitating hospitalization. Children in the propranolol group had more pulmonary events (typically upper respiratory tract infections) than those in the prednisolone arm (14 vs. 5, p<0.001). In one cohort study (poor quality for harms reporting) ulceration and atrophic scarring occurred in one child receiving propranolol and laser treatment, and no adverse effects were observed in the propranolol only arm.[117]

Harms most frequently reported with use of oral beta-blockers (propranolol, atenolol, nadolol) included sleep disturbances, cold extremities, gastrointestinal symptoms, and bronchial irritation (classified as hyperreactivity, bronchospasm, bronchiolitis, cold induced wheezing). One study [72] reported hypotension and bradycardia in three of 15 children, and two syncopal episodes in another child. No children receiving beta-blockers in comparative studies discontinued treatment due to adverse effects. Studies typically included a limited number of participants and may not have been adequately powered to detect harms (Table 21).

Table 21. Harms/adverse effects in comparative studies of beta-blockers to treat IH

Harm/Adverse Event	N Studies Reporting Harm (# Participants With Harm/Total Participants)	Reported Rates Across Studies
Propranolol 2-2.7 mg/kg/day		
Bronchial hyperreactivity[114]	1 (4/28)	14%
Bronchiolitis[13]	1 (4/19)	21%
Bronchospasm[73]	1 (1/31)	3%
Cold extremities[13, 112]	2 (7/39)	5%-30%
Constipation or gastrointestinal complaints[75, 112, 114]	3 (5/60)	5%-11%
Dental caries[13]	1 (1/19)	5%
Elevated alkaline[13]	1 (1/19)	5%
Hypoglycemia[76, 114]	2 (3/96)	1%-7%
*Hypotension[72, 75, 114]	3 (4/55)	4%-20%
Ulceration[13]	1 (1/19)	5%
Sleep disturbance (insomnia, drowsiness, restless sleep)[13, 73, 75, 112, 114]	5 (27/110)	6%-50%
Streptococcal infection[13]	1 (1/19)	5%
Syncopal attack[72]	1 (1/15)	7%
Viral gastroenteritis[13]	1 (1/19)	5%
**Viral upper respiratory infection[13, 76]	2 (2/87)	1%-5%
Poor feeding[112]	1 (2/20)	10%
Fever[76]	1 (2/68)	3%
Rash[76]	1 (2/68)	3%
Tachycardia[76]	1 (1/68)	1%
Intralesional propranolol 1 mg		
Pain/inconvenience of therapy[72]	1 (3/15)	20%
Atenolol 3mg/kg/day		
Hypotension[114]	1 (1/30)	3%
Restless sleep[114]	1 (8/30)	27%
Constipation[114]	1 (2/30)	7%
Diarrhea[114]	1 (2/30)	7%
Nadolol up to 4 mg/kg/day		
Cold extremities[79]	1 (2/10)	20%
Cold induced wheezing[79]	1 (1/10)	10%
Sleep disturbance[79]	1 (1/10)	10%
Gastrointestinal symptoms[79]	1 (5/10)	50%
Placebo		
Sleep disturbance[13]	1 (2/20)	10%
Ulceration[13]	1 (1/20)	5%
Visual compromise[13]	1 (1/20)	5%
Bronchiolitis[13]	1 (1/20)	5%

*One study[72] reported hypotension and bradycardia in 3/15 children.
**One study[76] reported upper respiratory infection and reactive airway disease in 1/68 children.
Abbreviations: IH = infantile hemangioma; n = number

The safety population in a large RCT[71] included 456 patients in total (Table 22). Thirty-three serious events occurred in 26 patients, and no significant difference overall or in individual events between the placebo group and group receiving propranolol at 3 mg/kg/day for 6 months were noted. One serious adverse event of second-degree atrioventricular heart block (with a preexisting cardiac condition later documented) occurred after dose administration on day 0 and treatment was discontinued. While hypotension and hypoglycemia were both documented in this trial, neither was clinically significant enough to lead to treatment discontinuation.

Table 22. Harms/adverse events reported by dose in Leaute-Labreze et al. 2015

Adverse Event	1 mg/kg/day X 3 months (n=98)	1 mg/kg/day X 6 months (n=102)	3 mg/kg/day X 3 months (n=100)	3 mg/kg/day X 6 months (n=101)	Placebo (n=55)
	N experiencing harm (%)				
≥1 Serious adverse event	5 (5)	3 (3)	9 (9)	6 (6)	3 (5)
≥1 Adverse event occurred during treatment	89 (91)	92 (90)	92 (92)	97 (96)	42 (76)
Hypotension	2 (2)	1 (1)	3 (3)	0 (0)	1 (2)
Bronchospasm	0 (0)	0 (0)	2 (2)	1 (1)	1 (2)
Bradycardia	0 (0)	1 (1)	1 (1)	0 (0)	0 (0)
Hypoglycemia	0 (0)	1 (1)	0 (0)	1 (1)	0 (0)
Diarrhea	16 (16)	14 (14)	17 (17)	28 (28)	4 (7)
Sleep disorder	28 (29)	14 (14)	19 (19)	22 (22)	7 (13)
Bronchitis	5 (5)	7 (7)	11 (11)	17 (17)	1 (2)
Vomiting	16 (16)	13 (13)	10 (10)	13 (13)	3 (5)
Bronchiolitis	6 (6)	7 (7)	6 (6)	10 (10)	3 (5)
Cold hands and feet	8 (8)	10 (10)	1 (1)	10 (10)	1 (2)
Agitation	12 (12)	18 (18)	8 (8)	7 (7)	6 (11)
Constipation	9 (9)	6 (6)	9 (9)	4 (4)	1 (2)
Decreased appetite	5 (5)	3 (3)	5 (5)	1 (1)	1 (2)
Somnolence	6 (6)	4 (4)	1 (1)	1 (1)	1 (2)

Abbreviations: n = number

Table 23 summarizes the incidence and type of adverse effects reported in case series. Consistent with the pharmacological action of propranolol, decreases in blood pressure and heart rate were the most frequently reported adverse events and were as high as 100 percent in some series.[135, 138] However, reductions in these parameters were not always clinically significant. In most prospective case series, clinically important hypotension and bradycardia were not reported; only asymptomatic changes were noted.[12, 118-125] The lack of cardiac events may be due to required cardiovascular evaluation prior to initiation of propranolol or discontinuation after short-term monitoring. The number of patients that did not qualify for propranolol therapy was not provided in any of these series. No adverse effects were reported in three prospective case series,[121, 123, 124] and most studies of topical beta-blockers reported that no adverse events were observed.[126, 127, 153] Two studies of topical applications reported recurrent itching[154] in 3 percent of children and sleep disturbances in 1 percent.[128] The remaining case series reported few adverse events. Those reported rarely caused discontinuation of the medication. In total, 40/ 2541 children in case series discontinued treatment due to adverse events including sleep disturbances (n=13), bronchial hyperreactivity, wheezing, or asthma (n=9), and cold extremities (n=7).

Table 23. Adverse effects in case series of propranolol to treat IH

Harm/Adverse Event	Number of Studies (# Participants With Harm/Total Participants)	Reported Rates Across Studies
Propranolol 1-1.5 mg/kg/day		
Decrease in heart rate and blood pressure[138]	1 (89/89)	100%
Elevation of liver enzymes (ALT, AST) [138]	1 (5/89)	6%
Hypoglycemia[138]	1 (4/89)	4.5%
Anorexia[122]	1 (1/35)	3%
Diarrhea[120]	1 (3/89)	3%

Harm/Adverse Event	Number of Studies (# Participants With Harm/Total Participants)	Reported Rates Across Studies
Asymptomatic hypotension[120]	1 (1/60)	2%
Nausea[138]	1 (2/89)	2%
Cold extremities[138]	1 (1/89)	1%
Restless sleep[138]	1 (1/89)	1%
Propranolol 2-2.1 mg/kg/day		
*Hypotension[14, 134, 135, 140]	4 (43/186)	2%-62%
ECG changes[134]	1 (7/25)	28%
Bradycardia[118, 134, 135, 140]	4 (18/222)	1%-24%
Nausea/Vomiting/Diarrhea[118, 120, 129, 142, 145, 146, 148]	8 (30/563)	0.53%-24%
Cold extremities[118, 130, 145, 147]	4 (11/260)	1%-10%
Sleep disturbance/Light sleep[120, 129, 132, 134, 146]	5 (9/194)	3%-10%
Behavioral changes[129, 134, 142, 145]	4 (8/287)	0.53%-10%
Respiratory symptoms/Asthma[118, 129, 130, 132, 145, 147]	6 (15/332)	2%-10%
Fatigue/Somnolence[132, 134, 140, 143, 147]	5 (8/262)	1%-7%
Fever[129]	1 (2/30)	7%
Gross motor abnormalities[142]	1 (13/188)	7%
**Hypoglycemia[135, 140]	2 (5/133)	2%-5%
Cutaneous symptoms/Rash[120, 143, 147]	3 (5/172)	2%-5%
Gastroesophageal issues[147]	1 (2/55)	4%
Sweating[14, 143]	2 (2/85)	2%-4%
Constipation[118]	1 (2/64)	3%
Respiratory tract infection[129]	1 (1/30)	3%
Skin atrophy[123]	1 (2/50)	3%
Seizure[137]	1 (1/45)	2%
Agranulocytosis[130]	1 (1/97)	1%
Cyanotic breath-holding spells[150, 151]	1 (1/71)	1%
Low body temperature[130]	1 (1/97)	1%
Stridor[150, 151]	1 (1/71)	1%
Recurrent bronchospasm[135]	1 (1/250)	0.4%
Propranolol 3-3.3 mg/kg/day		
***Sleep disturbances/Nightmares[125, 131, 133]	3 (14/99)	3%-23%
Transient asymptomatic hypotension[125, 131]	2 (7/66)	3%-17%
Daytime drowsiness[131]	1 (6/35)	17%
Benign infections[131]	1 (4/35)	11%
Digestive symptoms[131]	1 (3/35)	9%
Constipation[119]	1 (2/30)	7%
Tachypnea[119]	1 (2/30)	7%
Irritability[131]	1 (2/35)	6%
Cold extremities[119, 133]	2 (2/66)	3%
Esophageal reflux[125, 133]	2 (2/64)	3%
Poor weight gain[131]	1 (1/35)	3%
Decreased appetite[131]	1 (1/35)	3%
Bradycardia[131]	1 (1/35)	3%
Hypoglycemia[119]	1 (1/30)	3%
Increased appetite[131]	1 (1/35)	3%
Shortness of breath on activity[131]	1 (1/35)	3%
Propranolol 2-3 mg/kg/day		
Cold extremities[12, 139]	2 (64/206)	3%-36%
Nocturnal restlessness[139]	1 (39/174)	22%
Daytime sleepiness/Inactivity[139]	1 (28/174)	16%
Gastrointestinal symptoms[139]	1 (12/174)	7%
Agitation[12]	1 (2/32)	6%
Insomnia[12]	1 (2/32)	6%
Restlessness/Increased daytime activity[139]	1 (9/174)	5%
Hypotension[12, 139]	2 (7/206)	3%

Harm/Adverse Event	Number of Studies (# Participants With Harm/Total Participants)	Reported Rates Across Studies
Asthma/Wheezing[12, 139]	2 (18/206)	3%
Nightmares[12]	1 (1/32)	3%
Sweating[12]	1 (1/32)	3%
Feeding difficulties[139]	1 (3/174)	2%
Ulceration (onset/worsening)[139]	1 (4/174)	2%
Breath holding spells[139]	1 (2/174)	1%
******Propranolol 1-4 mg/kg/day**		
Somnolence[152]	1 (3/53)	6%
Hypoglycemia[152]	1 (1/53)	2%
Hypotension[152]	1 (1/53)	2%
Profound mottling of extremities[152]	1 (1/53)	2%
Severe bradycardia[152]	1 (1/53)	2%

*One study[135] also reported that 50/50 children had at least one low diastolic blood pressure, 38/50 had at least one low systolic blood pressure, and 7/50 had low diastolic, systolic blood pressure and heart rate (data not factored into table).
**One study[135] reported "lethargy, viral illness, and hypoglycemia" in 2/250 children (data not factored into table).
***One study[131] reported discontinuation of propranolol in 4/35 children because of "insomnia, nightmares, loss of energy." These data are not factored into the table.
****These adverse events were also considered serious by the study investigators.[152]
Abbreviations: ALT = alanine aminotransferase; AST = aspartate transaminase; kg = kilograms; mg = milligrams

Harms Reported in Package Insert Data

Hemangeol® is the only medication included in this review that has an FDA approved indication for infantile hemangioma. The safety of Hemageol® in pediatric patients has been reported in the medication package insert.[155]FDA medical review packages were not available for this medication. The most common adverse events, occurring in greater than 10% of infants, were sleep disorders, aggravated respiratory tract infections such as bronchitis and bronchiolitis associated with cough and fever, diarrhea, and vomiting.[155] In a study of pooled safety data (n=424), infants (63% aged 91-150 days) were treated with Hemangeol® 1.2 mg/kg/day or 3.4 mg/kg/day for 3 or 6 months. Treatment emergent adverse events occurring in 3% or greater in infants receiving the Hemangeol® 1.2 mg/kg/day (n=200) or Hemangeol® 3.4 mg/kg/day (n=224) compared to placebo were provided. Adverse events and frequencies for patients receiving Hemangeol® 1.2 mg/kg/day included: sleep disorders (17.5%), bronchitis (8%), peripheral coldness (8%), agitation (8.5%), diarrhea (4.5%), somnolence (5.0%), nightmare (2.0%), irritability (5.5%), decreased appetite (2.5%), and abdominal pain (3.5%). Adverse events and frequencies for patients receiving Hemangeol® 3.4 mg/kg/day (n=224) included: sleep disorders (16.1%), bronchitis (13.4%), peripheral coldness (6.7%), agitation (4.5%), diarrhea (6.3%), somnolence (0.9%), nightmare (6.3%), irritability (1.3%), decreased appetite (3.6%), and abdominal pain (0.4%). Additional adverse events reported in less than 1% of patients participating in clinical trials included: second degree atrioventricular heart block (occurring in a patient with underlying conduction disorder), urticaria, alopecia, decreased blood glucose, and decreased heart rate.

The safety and efficacy of the oral tablet, oral capsule, and injectable formulations of propranolol have not been investigated in pediatric patients.[156-158] The package inserts for these formulations state that reports of bronchospasm and congestive heart failure have been reported in pediatric patients receiving propranolol. Additional adverse events revealed during post-marketing surveillance include agranulocytosis, hallucination, and purpura.[155]

Harms of Other Active Comparator Agents

Harms of corticosteroids and PDL are presented in those sections; this section only includes medications for which harms are not presented elsewhere in this review. In a study rated poor quality for harms reporting, reported complications of bleomycin included febrile episode, superficial ulceration, and raised alkaline phosphatase.[74] The proportion of participants who experienced these complications is unclear. In another study, which was rated good quality for harms reporting, adverse effects in 20 participants using imiquimod included crusting of lesions (65%), superficial scars (15%), and skin pigmentation (29%).

Key Question 3. Effectiveness and Harms of Drugs Administered After the Failure of Corticosteroids or Beta-Blockers

We did not identify any studies addressing this Key Question.

Key Question 4. Effectiveness and Harms of Surgical Interventions

Key Points

- Studies addressed different laser modalities compared with observation or other laser modalities. No other surgical methods were evaluated in comparative studies. PDL was the most commonly studied laser type, but multiple variations in treatment protocols did not allow for demonstration of superiority of a single method (low SOE difference in effects on size reduction between long-pulse PDL and other lasers).
- Many 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 (low SOE for lack of difference between PDL and observation).
- Cohort studies assessed outcomes after CO_2 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 (insufficient SOE).
- 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 (moderate SOE for association of PDL with pigmentation changes; low for association with bleeding; and insufficient for scarring. Low SOE for association of Nd:YAG laser with scarring and insufficient for association with bleeding ad pigmentation changes).

Overview of the Literature

Nine comparative studies (three RCTs[159-161] and six retrospective cohort studies[162-167]) and 24 case series addressed surgical approaches. The RCTs were conducted in the Netherlands,[159] Japan,[160] and the UK.[161] Cohort studies were performed in the United States,[166, 168] Greece,[167] Singapore,[162] and Germany.[163, 164] Two RCTs[159, 161] compared PDL to observation; one used traditional PDL in infants aged 1 to 14 weeks,[161] and the second used PDL with epidermal

cooling in infants aged 0 to 6 months.[159] The third RCT[160] compared the use of non-cooled traditional PDL to long-pulse PDL with epidermal cooling in infants aged 1 to 3 months. We considered RCTs to be of good[159] and fair quality.[160, 161]

All of the cohort studies examined various comparisons between different laser types. Comparisons of different laser types included PDL vs. Nd:YAG,[164] Argon vs. Nd:YAG,[166] short pulse PDL vs. long-pulse PDL.[162] One compared Nd:YAG and CO_2 lasers and also included a non-surgical comparison group for airway IH.[163] Two studies compared different skin cooling protocols with the same laser types, including Nd:YAG[167] and PDL.[168] We considered two cohort studies as fair quality,[162, 167] and the rest as poor.[163, 164, 166, 168]

Overall, long 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 long pulse PDL compared to observation in managing the size of IH, although the magnitude of effect differed substantially. CO_2 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.

SOE for outcomes after laser treatments ranged from insufficient to low for effectiveness outcomes. The evidence was limited by low sample size, and variations in the laser settings used including wavelength and cooling protocols. For Nd:YAG and CO_2 lasers, all studies were limited by sample size, and SOE was insufficient for all outcome parameters.

Twenty-five case series reported on harms of surgical approaches for IH. Twelve case series reported on harms from laser treatments, including seven studies of PDL,[169-175] four studies of Nd:YAG lasers,[176-179] and one report of carbon dioxide laser.[180] Most studies included children with IH in multiple locations; one included children with only airway IH.[180]Ages of children in these series, where clearly reported, ranged from less than 1 month to 11 years. We considered one study to be of good quality for harms reporting,[171] one of fair quality,[175] and 10 of poor quality.[169, 170, 172-174, 176-180] We rated one cohort study that compared propranolol with concurrent PDL or followed by PDL as poor quality for harms reporting and discuss harms of PDL here and harms of propranolol in the beta-blocker section of KQ2 above.[117]

Thirteen case series (840 children) reported harms from surgical procedures, typically excision or resection, to treat IH.[181-192] Ages ranged from 1 month to 19 years. The majority of studies focused on treatment of facial IH, including three studies of lip IH,[183, 187, 191] two series of periocular/periorbital IH,[185, 188] two reports of various facial locations,[184, 190] and one study of nasal tip IH.[186] All of the studies were rated as poor quality for assessment of harms as data collection was not predefined.

Detailed Analysis

Effectiveness of Laser Treatment

PDL Compared With Observation

Two RCTs compared PDL to observation. One good quality RCT[159] randomized 22 children with IH between 0 and 6 months of age in the Netherlands into equal groups of observation or PDL with epidermal cooling. One patient in the laser group and two in the observation group were lost to followup. Outcomes were pre-specified as size change measured by serial photographs with a ruler and Visitrak Digital to measure surface area, depth measured by echo, and color measured by reflectance photometer. Blinded medical evaluators assessed these

outcomes at 3, 6, 9 and 12 months after treatment initiation. Twelve-month scores were used for analysis. Further, parents were asked to provide quality of life questionnaires at enrollment and at age 12 months. There was no statistical difference seen in echo depth or total surface area between the two groups; however color was significantly improved in the PDL group compared with control (p=0.03). Photographs reviewed for overall cosmetic improvement also showed a "significant improvement" for the PDL group (46%) over the observation group (18%), but this "significant improvement" was not quantitatively defined. Parent-reported quality of life scales showed no difference in the severity of skin problems between groups. Sixty-three percent of parents in the PDL group reported an improved cosmetic result at 12 months compared with 33% in the observation group (p=NR). Thirteen percent of parents perceived the treatments to be very painful.

The second, fair-quality RCT randomized 121 children to PDL (n=60) and observation (n=61) groups by telephone block randomization.[161] Outcomes of interest were evaluated at 1 year and pre-specified as clearance or near clearance (minimal residual signs) of the original lesion, perception of the hemangioma as a problem based on parental report, and harms. The investigators attempted to reduce bias by including a blinded panel of parents of non-study children to describe whether they perceived the hemangioma to be a problem at 1 year of age. Secondary outcomes were also graded by a blinded medical examiner at 1 year and consisted of overall surface area, height and redness of the lesion. The investigators reported no differences in the number of children experiencing near complete resolution (42%-44% in each group) but more children in the PDL group (30%) than in the control arm (5%) experienced complete resolution (p=0.001). Outcomes between groups were similar at the 5-year followup. Table 24 outlines key outcomes.

Table 24. Key resolution outcomes in studies comparing PDL and observation

Author, Year Groups (n) Quality	**Age, Months** **Type**	**Location**	**Methods and Measures of Resolution/ Response**	**Resolution Outcomes**
Kessels et al. 2013[159] G1: Pulsed dye laser (11) G2: Observation (11) **Quality:** Good	**Age, median (range)** G1: 3 (1.7-5.0) G2: 3 (1.5-4.5) **Type** Superficial and cutaneous only	G1+G2: multiple	• Photographs • Color measured by reflectance photometer • Improvement scale 1= no improvement 2= moderate improvement 3 = significant improvement	**Change in echo depth, median (interquartile range)** G1: -1.21 (-1.75 to 0.15) G2: -1.10 (-2.00 to 0.96) G1 vs.G2 p= 0.69 **Change in surface, median (interquartile range)** G1: 0.40 (0.10 to 0.80) G2: 0.00 (-0.08 to 0.40) G1 vs.G2 p= 0.08 **Color change, median (interquartile range)** G1: 10.16 (5.50 to 15.41) G2: 4.23 (0.84 to 5.28) G1 vs.G2 p= 0.03

Author, Year Groups (n) Quality	Age, Months Type	Location	Methods and Measures of Resolution/ Response	Resolution Outcomes
Batta et al. 2002[161] G1: Pulsed dye laser (60) G2: Observation (61) **Quality:** Fair	**Age, median (range, days** G1: 38 (10 to 101) G2: 32 (5 to 79) **Type, n (%)** Flat G1: 31 (52) G2: 30 (49) Raised G1: 29 (48) G2: 31 (51)	G1+G2: multiple	• Photographs • Primary outcome measure: complete clearance or minimum residual signs at age 1 year	**Complete clearance or minimum residual signs, n (%)** G1: 25 (42) G2: 27 (44) G1 vs.G2: p=0.92 Complete only G1: 18 (30) G2: 3 (5) G1 vs.G2: p=0.001

Abbreviations: G = group; n = number

Comparative Effectiveness of Various PDL Modalities

One fair quality Japanese RCT[160] randomized 52 patients to a "traditional PDL" group and a "long-pulse dye laser" group. Patients in the traditional PDL arm were treated with a 585nm laser with the following settings: spot size: 7mm, fluence: 6 to7 J/cm^2, and pulse duration: 0.45 milliseconds. Patients in the long pulse PDL group were treated with a 595nm laser with the following settings: spot size: 7mm, fluence: 9 to 15 J/cm^2, and pulse duration: 10-20 milliseconds. This group also received cryogen spray cooling. All patients were followed up with serial photographs and analyzed at 1 year for clearance rates, time to maximal proliferation and complications. A blinded medical evaluator performed the scoring. The percentage of patients achieving an excellent (76-100%) clearance of the lesion did not differ between groups, with rates of 54 to 65 percent in each group. Time to maximal proliferation was significantly shorter (106 days) in the long pulse PDL group compared with the traditional PDL group (177 days, p=0.01). Another fair quality cohort study comparing short and long pulse PDL similarly reported no significant differences in the number of children with complete or near-complete resolution by age 3 to 3.5 years.[162]

In a poor quality cohort study evaluating cryogen spray cooling as an adjunct to PDL vs. no cooling in 164 children (mean age overall= 2 years, 11 months), investigators assessed changes in color, texture, and volume, graded on a scale of 1(poor) to 4(excellent) by blinded, experienced plastic surgeons.[168] Children in the cryogen cooling arm required fewer treatments and had greater improvements in volume and texture than children in the non-cooled PDL arm (p values <0.01). Changes in color did not differ between groups. Table 25 outlines key outcomes.

Table 25. Key resolution outcomes in studies comparing PDL modalities

Author, Year Groups (n) Quality	Age, months Type	Location	Methods and Measures of Resolution/Response	Resolution Outcomes
Kono et al. 2005[160] G1: Long-pulse dye laser (26) G2: Traditional pulsed dye laser(26) **Quality:** Fair	**Age, mean±SD, weeks** G1: 11.2 G2: 10.7 **Type, % Superficial** G1+G2: 100	G1+G2: multiple	• Serial photographs assessed using: Excellent: 76-100% Moderate: 51-75% Mild: 26-50% None or worse (0-25%)	**Complete clearance or minimal residual signs at 1 year, n (%)** G1: 17 (65) G2: 14 (54) G1 vs.G2 p=0.397 Excellent G1: 17 G2: 14 Moderate G1: 7 G2: 5 Mild G1: 2 G2: 4 None or worse G1: 0 G2: 3
Tay et al. 2012[162] G1: Short pulse 595-nm Pulsed dye laser (15) G2: Long-pulse 595-nm PDL (8) **Quality:** Fair	**Age mean (range)** G1+G2: 6.5 (2.5-19) **Type, n** Superficial G1: 7 G2: 3 Mixed G1: 8 G2: 5	**G1+G2:** multiple	• Photographs	**Number of treatments needed for resolution** G1: 3-14 mean=8 median=7 G2: 4-14 mean=9 median=7 G1 vs.G2: p=ns Average number of treatments needed for the clearance of mixed IH= 4 to 5 treatments more in both groups
Chang et al. 2001[168] G1: Non cooled flash lamp-pumped pulsed dye laser (82) G2: Cryogen spray cooling plus flash lamp-pumped pulse dyed laser (82) **Quality:** Poor	**Age, mean, years** G1: 2.5 G2: 3.4 **Type, %** Cutaneous G1+G2: 100	**G1+G2:** multiple	• Volume reduction, texture, color	**Volume reduction, mean score** G1: 3.84 G2: 3.96 G1 vs.G2 p=0.008 **Texture** G1: 3.57 G2: 3.90 G1 vs.G2 p=0.001 **Color** G1: 3.98 G2: 4.00 G1 vs.G2 p=0.155

Abbreviations: G = group; n = number; PDL = pulsed dye laser; SD = standard deviation

Nd:YAG Laser Compared With Other Lasers or Observation

Three poor quality cohort studies compared Nd:YAG laser to either Argon laser,[166] traditional PDL,[164] or CO_2 laser or observation.[163] One study included 55 children with sequelae from hemangioma and reported similar rates of excellent clearance (defined as 90-100% clearance) between Nd:YAG and Argon groups and a higher rate of children attaining 50 percent or greater clearance in the Nd:YAG group (72% vs. 52%).[166] Lesions were also scored for size length and width, which showed little difference between groups. Heights of lesions were sub-analyzed, which showed a greater ability of Nd:YAG to treat thicker lesions, with no excellent results in the argon group for lesions 0.5 cm in height and greater.

In a study comparing Nd:YAG and PDL and including 50 children, 41 percent of children receiving PDL and 30 percent receiving Nd:YAG had complete clearance of IH (p=NR).[164] Similar numbers in each group had 70 to 99 percent or <70 percent clearance, and 7 percent in the PDL arm and 18 percent in the Nd:YAG arm had growth of IH. The average pain score was 5.6 for the PDL group and 3.9 for the Nd:YAG arm.

A final retrospective cohort reviewed outcomes after practice changes regarding the management of subglottic hemangioma.[163] Fifteen children in the "pre-laser" era (1973-1986) were treated with observation and systemic steroids, 14 patients from 1986-1994 were treated with Nd:YAG, and 17 patients from 1995 and after were treated with CO_2 laser. All patients with severe airway obstruction from the hemangioma were treated with tracheostomy. Further the data were analyzed for complications from the treatment method itself, including the secondary need for tracheostomy from laser induced scarring. In children who did not present with previously placed tracheostomy, there was no statistical difference in the need for tracheostomy between the steroid treatment group and the Nd:YAG group; however, CO_2 yielded a lower tracheostomy rate. There was also a reduction in the time to tracheostomy decannulation from 26.6 to 10.6 months with CO_2 compared with Nd:YAG. There was no difference in time to decannulation with Nd:YAG compared to steroid treatment. Two of 10 Nd:YAG patients developed laser-related stenosis; no patients in the CO_2 group developed stenosis. Speech and developmental issues were reported by more parents of children who had had tracheostomy compared with those who had no tracheostomy, and parental worry about the fate of the child lessened earlier if the child did not have a tracheostomy. Table 26 outlines key outcomes.

Table 26. Key resolution outcomes in comparative studies of Nd:YAG laser

Author, Year Groups (n) Quality	Age, months Type	Location	Methods and Measures of Resolution/Response	Resolution Outcomes
Achauer et al. 1989[166] G1: Argon (30) G2: Nd:YAG (25) **Quality**: Poor	**Age** G1+G2: range 2 weeks to 5 years **Type** NR	G1+G2: multiple	• % reduction in volume graded: Excellent: 90-100% Good: 51-89% Fair: 25-50% Poor: 0-24%	**Volume reduction, %** Excellent G1: 35 G2: 44 Good G1: 17 G2: 28 Fair G1: 21 G2: 12 Poor G1: 17 G2: 2
Raulin et al. 2001[164] G1: Flashlight pumped pulsed dye laser (25) G2: Long-pulse Nd:YAG laser (25) **Quality:** Poor	**Age** NR **Type, %** Superficial **G1+G2:** 100	G1+G2: multiple	• Photographs • Regression rated as 100%, 70-99%, <70%	**Regression, n of IH (%)** 100% G1: 11/29 (41) G2: 7/33 (30) 70-99% G1: 14/29 (52) G2: 13/33 (57) < 70% G1: 2/29 (7) G2: 3/33 (13)
Nicolai et al. 2005[163] G1: No laser (14) G2: Nd:YAG laser (14) G3: CO_2 laser (17) **Quality:** Poor	**Age** NR **Type** NR	G1+G2+G3: airway	• Resolution not assessed	**Other outcomes** • Reduced time to decannulation in G3 vs. G2 • 12/16 children across groups who had tracheostomy had delayed speech development that improved after decannulation; no speech delays in children without tracheostomy • 7/16 tracheostomized children had motor delay vs. 1/16 without tracheostomy • Parental worries about fate of child lessened roughly 2 years earlier for parents of children without tracheostomy vs. parents of those with tracheostomy

Abbreviations: G = group; IH = infantile hemangioma; n = number; NR = not reported; Nd:YAG = neodymium yttrium aluminum garnet ; SD = standard deviation

Nd:YAG Laser With Cooling Compared with No Cooling

In one fair quality cohort study, 235 patients (mean age= 9 months) received the same Nd:YAG laser treatment but different methods of epidermal cooling (ice chips during procedure,

n=115; ice before, during, and after treatment, n=120).[167] Children were treated until they received an excellent (90-100% resolution) or good (50-89% resolution) result. Patients with more extensive cooling required a mean 1.45 sessions of laser treatment compared to 2.11 in the less extensive cooling group (Table 27).

Table 27. Key resolution outcomes in comparative studies of Nd:YAG laser with cooling

Author, Year Groups (n) Quality	Age, months Type	Location	Methods and Measures of Resolution/Response	Resolution Outcomes
Vlachakis et al. 2004[167] G1: Nd:YAG laser, cooled with ice before, during and after irradiation (120) G2: Nd:YAG laser, cooled with ice only during irradiation (115) **Quality:** Fair	**Age mean (range)** G1+G2: 9 (3 mos to 4 years) **Type, %** Cutaneous G1+G2: 100	G1+G2: multiple	• Change in size Excellent: 90-100% area reduction Good: 50-89% Moderate: 20-49% Poor: 0-19%	**Total resolution after session 1** G1: 65 G2: 39 **Total resolution after session 2** Excellent G1: 55/55 G2: 24/76 Good G1: 0 G2: 52/76

Abbreviations: G = group; n = number; Nd:YAG = neodymium yttrium aluminium garnet

Harms of Surgical Interventions

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. In one RCT comparing traditional PDL and long-pulse PDL, hyperpigmentation, hypopigmentation, and negative textural changes were all significantly greater in the traditional PDL group (p values <0.01).[160] In a cohort study comparing short and long-pulse PDL, minor skin complications were greater in the short pulse group, and typical sequelae or laser treatment, erythema, edema and purpura, lasted longer in the short pulse group, but the study did not provide statistical analysis of these outcomes.[162] Studies typically included a limited number of participants and may not have been adequately powered to detect harms. Table 28 outlines harms reported in comparative studies.

Table 28. Harms/adverse effects in comparative studies of lasers to treat IH

Harm/Adverse Event	N Studies Reporting Harm (# Participants With Harm/Total Participants)	Reported Rates Across Studies
Pulsed dye laser		
Purpura[164]	1 (25/25)	100%
Swelling[164]	1 (25/25	100%
Skin atrophy[161]	1 (17/60)	28%
Minimal crusting[159]	1 (2/11)	18.2%
Ulceration[161]	1 (4/60)	7%
Painful ulceration[161]	1 (3/60)	5%

Harm/Adverse Event	N Studies Reporting Harm (# Participants With Harm/Total Participants)	Reported Rates Across Studies
Ulcer formation[160]	1 (1/26)	4%
Bleeding[161]	1 (2/60)	3%
Infection[161]	1 (2/60)	3%
*Atrophic scarring[117, 164]	1 (2/42)	3%-6%
Hyperpigmentation[160, 162, 164]	3 (12/66)	13%-20%
Texture change[160, 162]	2 (8/41)	13%-23%
Hypopigmentation[160-162, 164]	4 (41/126)	10%-45%
Blistering (crusts and blisters)[162, 164]	2 (21/40)	13%-76%
Long-pulse PDL		
Hypopigmentation[160, 162]	2 (4/34)	12%-12.5%
Hyperpigmentation[160, 162]	2 (3/34)	8%-12.5%
Texture change[160, 162]	2 (2/34)	4%-12.5%
Nd:YAG laser		
Hypopigmentation[164]	1 (2/25)	6%
Purpura[164]	1 (5/25)	20%
Crusts and blisters[164]	1 (8/25)	24%
Swelling[164]	1 (25/25	100%
Atrophic scarring[164]	1 (1/25)	3%
Scarring[166]	1 (8/26)	30.8%
Delayed healing[166]	1 (1/26)	12.5%
Postoperative bleeding[166]	1 (2/26)	7.7%
Postoperative complications (including bleeding, atrophic scars and hypertrophic scars)[167]	1(35/235)	14.9%
Argon laser		
Delayed healing[166]	1 (2/31)	13%
Postoperative bleeding[166]	1 (1/31)	3.2%
Reaction to local anesthesia (seizure and hospitalization) [166]	1 (1/31)	3.2%
Observation		
Hypopigmentation[161]	1 (9/61)	15%
Skin atrophy[161]	1 (5/61)	8%
Ulceration[161]	1 (4/61)	7%
Painful ulceration[161]	1 (2/61)	3%
Bleeding[161]	1 (2/61)	3%
Infection[161]	1 (4/61)	7%

*One study reported atrophic scarring and ulceration in 1/17 children receiving PDL and concurrent propranolol.[117] One study (not represented in table) reported that 12.4% of the parents of 11 children receiving PDL judged that the treatment was painful.
Abbreviations: IH = infantile hemangioma; n = number; Nd:YAG = neodymium yttrium aluminum garnet; PDL = pulsed dye laser

Seven case series reported on 537 children who were treated with PDL (Table 29). One Korean study (good quality for harms reporting) treated 47 superficial or mixed IH in 40 patients monitored for hyper- and hypo- pigmentation, skin atrophy, hypertrophic scarring, and ulceration during treatment.[171] The only adverse event noted in this study was hyperpigmentation in two patients with superficial IH. The final assessment in this study was at the end of treatment so no long term follow information was available. A fair quality case series reported on PDL treatment for 65 children with ulcerated IH.[175] There were no cases of the predefined complications of hypo- or hyperpigmentation or epidermal textural changes. Some scarring occurred in an unknown number of patients that was comparable to scarring associated with healing of conservative treatment. The most frequently reported harms were hyperpigmentation (1% to 14% in four studies[169, 171-173]) and hypopigmentation (0-14% in four studies[169, 171-173]). Ulceration and

blistering were also noted in one study each. Two studies reported no adverse events,[170, 174] and another reported no permanent side effects but cases of hyper and hypopigmentation.[173]

One thousand and seven children received treatment with Nd:YAG lasers reported in four case series. The most frequently reported adverse events from one large case series with 684 children included skin burn (11%), infection (6.6%), and scarring (4.4%).[177] Another larger study with 160 participants reported complications including delayed healing, postoperative infection and scarring in 10 percent of their patients.[176] A single case series of 31 patients with subglottic IH noted one case of respiratory distress related to the ventilation system.[180] Table 29 outlines harms in these studies.

Table 29. Adverse effects in case series of laser treatments for IH

Harm/Adverse Event	Number of Studies (# Participants With Harm/Total Participants)	Reported Rates Across Studies
Pulsed dye laser		
Hyperpigmentation[169, 171-173]	4 (17/357)	1%-14.5%
Hypopigmentation[169, 171-173]	4 (27/357)	0-14%
Ulceration[172]	1 (1/90)	1%
Blisters[169]	1 (3/62)	4.8%
Nd:YAG laser		
Scarring[177, 179]	2 (36/794)	4.4%-5.5%
Hypertrophic scarring[179]	1 (2/110)	1.8%
Ulceration[177]	1 (15/684)	2.2%
Skin burn[177]	1 (75/684)	11%
Bleeding[177, 179]	2 (13/794)	0.9%-1.8%
Nerve injury[177]	1 (9/684)	1.3%
Infection[177]	1 (45/684)	6.6%
Undesirable texture change[177]	1 (30/684)	4.4%
Anemia and hyperkalemia[177]	1 (1/684)	0.15%
Postoperative stenosis[178]	1 (1/53)	1.9%
CO_2 laser		
Respiratory distress[180]	1 (1/31)	3.2%
Subglottic scarring[180]	1 (1/31)	3.2%

One study[175] noted "some" scarring. One study[176] reported complications of "delayed healing, infection and/or scar formation" in 16/160 (10%) of participants.
Abbreviations: CO_2 = carbon dioxide; Nd:YAG = neodymium yttrium aluminum garnet

Table 30 outlines harms reported in surgical case series. Dehiscence rates ranged from 1.4 percent to 5.5 percent in five studies,[181, 183, 189, 191, 193] and single cases of postoperative trauma-related wound dehiscence were reported in an additional three studies.[181, 184, 186] Postoperative infections were noted in two studies.[183, 192] Scarring, skin necrosis, and alopecia were also noted in two reports. Other complications including facial paresis, permanent palsy, hematoma, intraoperative bleeding, cellulitis, hypopigmentation were reported in a single study each. One study reported no adverse events.[190] One larger series of 127 patients with lip IH treated with liquid nitrogen cryotherapy reported five cases of hypopigmentation and three cases of hemorrhage and ulceration. Labial mucoceles were noted in three children three years after treatment.[187]

Table 30. Adverse effects in case series of surgical treatments for IH

Harm/Adverse Event	Number of Studies (# Participants With Harm/Total Participants)	Reported Rates Across Studies
Surgery including excision and resection		
Dehiscences[181, 183, 189, 191, 193]	5 (17/357)	1.4%-5.5%
Postoperative traumatic wound dehiscence [181, 184, 186]	3 (3/119)	2.3%-2.8%
Wound infections minor or dehiscence[184]	1 (6/44)	13.6%
Postoperative infection[183, 192]	2 (1/264)	0-2%
Postoperative hematoma[188]	1 (1/67)	1.5%
Intraoperative bleeding[192]	1 (2/50)	4%
Skin necrosis [186, 188]	2 (3/106)	2.6%-3%
Hypertrophic scarring/cheloids [192, 193]	2 (10/142)	4%-9.8%
Incomplete excision with scarring[192]	1 (1/50)	2%
Facial paresis, transient postop[182]	1 (4/43)	9.3%
Permanent palsy of facial nerve[182]	1 (1/43)	2.3%
Hemorrhage and ulceration[187]	1 (3/127)	2.4%
Hypopigmentation of the skin or vermillion of the lip[187]	1 (5/127)	3.9%
Labial mucoceles observed 3 years post- surgery[187]	1 (3/127)	2.4%
Alopecia/Loss of small eyelash segment[185, 193]	2 (2/125)	1.1%-3%
Cellulitis[193]	1 (2/92)	2.2%
Functional impairment[193]	1 (2/92)	2.2%

No complications were noted in one study.[190]

Discussion

State of the Literature

We identified 111 unique studies (12 randomized controlled trials [RCTs], five prospective and 15 retrospective cohort studies, two diagnostic accuracy studies, and 77 case series) addressing our Key Questions. Thirty-four comparative studies reported effectiveness outcomes (6 good quality, 18 fair quality, and 10 poor quality). One-hundred and eight studies (comparative studies and case series) reported harms/adverse events data (14 good quality for harms reporting, two fair quality, 92 poor quality). Fifty-seven studies addressed beta-blockers; 21 addressed lasers; 18 addressed steroids; 13 addressed surgical approaches; and two addressed diagnostic modalities.

The literature on pharmacologic and surgical approaches for the treatment of infantile hemangioma (IH) is heterogeneous in terms of populations, interventions, comparators, and outcomes. Comparative studies included individuals with ages of less than one month to over 40 years, and lesion types and locations varied across studies. Most studies included children with IH in multiple anatomic locations and of multiple types (e.g., deep, superficial) without stratifying outcomes on these characteristics. Studies typically did not clearly describe diagnostic criteria, and few clearly noted whether prior treatment had been administered (n=7/34 comparative studies).

Studies assessed varied pharmacologic agents (corticosteroids, beta-blockers, immunomodulators) administered through various routes (topical, intralesional, intravenous, oral) at multiple doses and durations as well as varied forms of laser treatment (e.g., pulsed dye laser [PDL], argon laser, neodymium yttrium aluminum garnet [Nd:YAG] laser) using varied regimens. No comparative studies addressed surgical treatment aside from laser modalities. Comparators also varied across studies and included placebo, observation, historical control groups, and other active interventions. Outcome measures similarly differed. While studies generally assessed change in lesion size or appearance, scales and methods varied and included visual analog scales, assessment of percentage size change, and more subjective assessments of good, fair, or poor response.

Summary of Key Findings

Until fairly recently, corticosteroids were the treatment of choice for IH. As reported in this review, corticosteroids demonstrate some effectiveness but may be associated with clinically significant 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/observation, to corticosteroids and other modalities, and to other beta-blockers. Relative to observation or placebo arms, 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 with the exception of no significant differences in reducing lesion size in two studies comparing it to steroids. 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, early results are as positive as those noted for propranolol, and we believe that they suggest that these and potentially other beta-blockers may also be effective, potentially with fewer side effects. These findings, however,

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 specifically, the expected efficacy of control arms was estimated to be 2 percent (95% Bayesian credible interval [BCI]=0% to 5%). All non-control treatments were estimated to have a larger expected clearance than control arms. The largest mean estimate of expected clearance was for oral propranolol (95%, 95% BCI: 86% to 100%), followed by timolol (64%, 95% BCI: 31% to 90%) and triamcinolone (53%, 95% BCI: 14% to 97%) albeit with wider confidence bounds. Oral steroids had a clearance rate of 29 percent (95% BCI: 9% to 50%). 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 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 review specific findings and strength of evidence (SOE) by key question and provide more detailed results from our meta-analysis below.

KQ1. Effectiveness and Harms of Imaging

Two poor quality diagnostic accuracy studies addressed imaging modalities.[50, 52] 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. 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 (Table 31), using weaker study designs and precluding a meta-analysis. The studies did not address harms.

Table 31. Strength of evidence for effectiveness of imaging modalities

Intervention/ Outcome **Study Design** Quality and Number of Studies (N Total)	**Study Limitations**	**Consistency**	**Directness**	**Precision**	**Reporting Bias**	**Finding** **Strength of Evidence Grade**
MRI vs. Ultrasound						
Accuracy in detecting spinal anomalies Cohort studies: 1 poor[50] (48)	High	Unknown	Direct	Imprecise	NA	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 given small, single, poor quality study.

MRI vs. Ultrasound vs. CT						
Accuracy in detecting liver IH Cohort studies: 1 poor[52] (55)	High	Unknown	Direct	Imprecise	NA	Ultrasound detected lesions in 42/44 children (95% sensitivity). Insufficient SOE given single small, poor quality study.

Abbreviations: CT = computed tomography; IH = infantile hemangioma; MRI = magnetic resonance imaging; n = number; NA = not applicable; SOE=strength of evidence

KQ2. Effectiveness and Harms of Corticosteroids and Beta-Blockers

Effectiveness and Harms of Corticosteroids

We identified 18 studies (three RCTs, one cohort study, and 14 case series) reporting outcomes and/or harms following corticosteroid use in children with IH.[33, 85-101] 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. Children in treatment arms typically had improvement in lesion size. Of the 219 children who received steroids in three studies[86, 101, 194] reporting such data, 140 had a "good" or "fair" response to steroids. In our network meta-analysis, oral steroids had a mean estimated expected clearance rate of 29 percent (95% BCI: 9% to 50%). The rate intralesional triamcinolone had a rate of 53 percent but with wide confidence bounds (95% BCI: 14% to 97%).

Thus, there is adequate evidence to support a moderate strength of evidence for oral steroids to have a modest effect on clearance rates and low SOE for intralesional steroids to have a modest (albeit larger) effect relative to control with wide confidence bounds.

However, steroids were consistently associated with clinically important harms including Cushingoid appearance, infection, growth retardation, hypertension, and mood changes that may be important in making treatment decisions. The SOE is moderate for the association of steroids with these clinically important harms (Table 32).

Table 32. Strength of evidence for effectiveness and harms of steroids

Intervention/ Outcome **Study Design** **Quality and Number of Studies (N Total)**	**Study Limitations**	**Consistency**	**Directness**	**Precision**	**Reporting Bias**	**Finding** **Strength of Evidence Grade**
Oral steroids vs. Observation or Placebo						
Improvement in IH Network meta-analysis	High	Consistent	Indirect	Imprecise	Undetected	In network meta-analysis oral steroids had a mean expected clearance rate of 29% compared with 2% for placebo/observation arms. Moderate SOE for greater effectiveness of oral steroids vs. placebo/observation given low precision.

Intralesional steroids vs. Observation or Placebo						
Improvement in IH Network meta-analysis	High	Consistent	Indirect	Imprecise	Undetected	In network meta-analysis intralesional steroids had a mean expected clearance rate of 53% compared with 2% 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						
Clinically important harms (Cushingoid facies, growth retardation, mood changes /irritability, hypertension, infection) RCT: 2 good[78, 85] 1 poor[101] (138) Cohort: 3 poor[33, 75, 76] (179) Case series: 9 poor[87, 88, 90, 91, 93-96, 99] (2944)	High	Consistent	Direct	Precise	NA	Studies consistently reported these adverse effects. Moderate SOE for the association of steroids with clinically important harms.

Abbreviations: n = number; NA = not applicable; RCT = randomized, controlled trial; SOE = strength of evidence

Effectiveness and Harms of Beta-Blockers

Fifty-seven studies (19 comparative studies and 38 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 2 percent (95% BCI: 0% to 5%) in placebo or observation arms, oral propranolol had a rate of 95% (95% BCI: 86% to 100%). With adequate data and good precision, we considered the SOE to be high for the effect of propranolol on lesion size relative to observation or placebo arms. 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 SOE to be low for an equivalent response of propranolol and nadolol or atenolol based on three small studies. We considered SOE to be low for greater effectiveness of topical timolol compared with observation or placebo (Table 33).

Table 33. Strength of evidence for effectiveness of beta-blockers

Intervention/ Outcome **Study Design** **Quality and Number of Studies (N Total)**	**Study Limitations**	**Consistency**	**Directness**	**Precision**	**Reporting Bias**	**Finding** **Strength of Evidence Grade**
Propranolol vs. Placebo or Observation						
Improvement in IH Network meta-analysis RCT: 2 good [13, 71] (496) Cohort studies: 1 fair[73] (45)	Low	Consistent	Indirect	Precise	Undetected	In network meta-analysis, the mean expected clearance rate for oral propranolol was 95% relative to 2% 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.
Rebound growth/Need for additional treatment RCT: 1 good[71] (456) Cohort studies: 1 fair[73] (45)	Low	Consistent	Direct	Precise	Un-detected	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.
Propranolol vs. Steroids						
Improvement in IH Network meta-analysis RCT: 1 good[78] (19) Cohort studies: 2 fair, 1 poor[75-77] (156)	High	Inconsistent	Indirect	Precise	Undetected	In head-to-head comparisons, propranolol more effective than steroids in two studies[75, 76]; two other studies reported no significant difference between propranolol and steroids.[77, 78]. In a network meta-analysis, puling data from multiple studies, propranolol was clearly superior to oral steroids (95% clearance versus 29% clearance). Combined effects from individual studies and meta-analysis confer moderate SOE for superiority of propranolol over steroids at achieving clearance.
Propranolol vs. Other beta-blocker						

Improvement in IH Network meta-analysis RCT: 1 fair[80] (23) Cohort studies: 1 fair, 1 poor[79, 113-115] (77)	High	Consistent	Indirect	Im-precise	Undetected	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 equivalent response with propranolol, nadolol, or atenolol (systemic beta-blockers) based on few, small studies.
Topical timolol vs. Placebo or Observation						
Improvement in IH Network meta-analysis RCT: 1 good[83] (41) Cohort studies: 1 fair, 1 poor [81, 82] (147)	Med-ium	Consistent	Indirect	Precise	Undetected	Timolol more effective than placebo or observation in three comparative studies. In network meta-analysis, the mean expected clearance rate for topical timolol was 64% relative to 2% for placebo or observation arms. Low SOE for effectiveness of timolol vs. placebo or observation based on the need for additional studies.

Abbreviations: IH = infantile hemangioma; N = number; RCT = randomized controlled trial; SOE = strength of evidence

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, cold induced wheezing). Harms generally were not severe enough to cause treatment discontinuation (n=40/2541 children in case series and no children in comparative studies). We considered the SOE to be moderate for the association of propranolol with clinically important and minor harms (Table 34).

Table 34. Strength of evidence for harms of beta-blockers

Intervention/ Outcome Study Design Quality and Number of Studies (N Total)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Finding Strength of Evidence Grade
Propranolol (topical, oral, intralesional)						
Clinically important harms (hypotension, bradycardia, bronchospasm, hypoglycemia) RCT: 2 good, 2 poor[13, 71, 72, 78] (560) Cohort studies: 3 poor[73, 76, 114] (213) Case series: 1 good, 4 poor[12, 120, 138, 139, 152] (657)	High	Consistent	Direct	Precise	Undetected	Rates of these harms with propranolol ranged from 0 to 100% across studies. Moderate SOE for association of propranolol with these harms.
Minor harms (cold extremities, diarrhea, sleep changes) RCT: 1 good, 2 poor[13, 71, 78] (515) Cohort studies: 4 poor[73, 75, 112, 114] (167) Case series: 1 good, 3 poor[12, 138, 139, 152] (597)	High	Consistent	Direct	Precise	Undetected	Rates of these harms with propranolol ranged from 1% to 50% across studies. Moderate SOE for association of propranolol with these harms.
Timolol						
Lack of harms RCT: 1 good[83] (41) Cohort studies: 1 good, 2 poor[81, 82, 84] (185)	Medium	Unknown	Direct	Im-precise	Undetected	No harms observed with timolol in 4 studies. Low SOE for lack of association of timolol with harms based on few studies.
Nadolol						

***Clinically important harms (hypotension, bradycardia, bronchospasm, hypoglycemia*)** Cohort studies: 1 poor [79] (19)	High	Unknown	Direct	Im-precise	NA	Harms of nadolol reported in 10%-20% of children**.** Insufficient SOE for association with clinically important harms given single, small poor quality cohort study.
Minor harms (cold extremities, diarrhea, sleep changes) Cohort studies: 1 poor[79] (19)	High	Unknown	Direct	Im-precise	NA	Harms of nadolol reported in 10%-50% of children**.** Insufficient SOE for association with minor harms given single, small poor quality study.
Atenolol						
Hypotension Cohort studies: 1 poor[114] (58)	High	Unknown	Direct	Im-precise	NA	Hypotension reported in 3% of children in one study. Insufficient SOE for association with hypotension given only a single, small poor quality study.
Minor harms (cold extremities, diarrhea, sleep changes) RCT: 1 poor[80] (23) Cohort studies: 1 poor[114] (58)	High	Consistent	direct	Im-precise	Undetected	Minor hams occurred in 7%-27% of children. Low SOE for the lack of association with minor harms given two small studies with high limitations.

Abbreviations: IH = infantile hemangioma; n = number; NA = not applicable; RCT = randomized, controlled trial; SOE = strength of evidence

KQ3. Effectiveness and Harms of Second-Line Drugs

We did not identify any studies addressing this question.

KQ4. Effectiveness and Harms of Surgical Interventions

Effectiveness and Harms of Laser Treatment

Nine comparative studies (three RCTs[159-161] and six retrospective cohort studies[162-167]) and 24 case series addressed surgical approaches.[169-192]Most comparative studies were small (≤55 participants), but one RCT and two 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. All studies except one reported on treatment of cutaneous lesions.

Overall, long 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 long pulse PDL compared to observation in managing the size of IH, although the magnitude of effect differed substantially. CO_2 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.

Strength of evidence for outcomes after laser treatments ranged from insufficient to low for effectiveness outcomes. The evidence was limited by low sample size, and variations in the laser settings used including wavelength and cooling protocols. For Nd:YAG and CO_2 lasers, all studies were severely limited by sample size, and SOE was determined to be insufficient in all outcome parameters (Table 35).

Table 35. Strength of evidence for effectiveness of laser modalities

Intervention/ Outcome **Study Design** **Quality and Number of Studies (N Total)**	**Study Limitations**	**Consistency**	**Directness**	**Precision**	**Reporting Bias**	**Finding** **Strength of Evidence Grade**
Long-pulse PDL vs. other laser types and protocols						
Improvement in IH RCT: 1 fair[160] (52) Cohort studies: 2 poor[164, 168] (212)	Medium	In-consistent	Direct	Imprecise	Undetected	In 1 RCT, resolution outcomes similar between laser types; greater clearance in PDL +cooling arm in one cohort study,[168] and more children in PDL arm had complete regression than in Nd:YAG in another[164]; typically more than 50% of children receiving any laser had at least 50% clearance. Low SOE for no difference in effects on size reduction between long-pulse PDL and various other lasers.
PDL vs. Observation						
Improvement in IH RCT: 1 good, 1 fair[159, 161] (143)	Low	Consistent	Direct	Imprecise	Suspected	No significant difference in measured volume or proportion of clearance between groups in either study when considering complete and near complete clearance; greater observer-ratings of cosmetic improvement for PDL arm vs. observation in one study.[159] Low SOE for lack of difference between PDL treatment and observation in reducing lesion size.

Quality of life RCT: 1 good, 1 fair[159, 161] (143)	Medium	In-consistent	Indirect	Imprecise	Undetected	No significant differences in parent ratings of QoL in one study; more parents of children in PDL arm in another considered cosmetic appearance improved than in observation arm. Low SOE for lack of difference in QoL with PDL compared with observation.
Nd:YAG with extended cooling vs. Nd:YAG with standard cooling						
Improvement in IH Cohort studies: 1 fair[167] (290)	Medium	Unknown	Direct	Imprecise	NA	Improved resolution with extended cooling protocol vs. traditional. Insufficient SOE given single study with medium limitations.
Nd:YAG vs. CO_2 laser vs. Tracheostomy						
Speech Cohort studies: 1 poor[163] (46)	High	Unknown	Indirect	Imprecise	NA	75% of children with tracheostomy had delayed speech vs. 0 with no tracheostomy in the laser treatment era. Insufficient SOE given small, single study

Abbreviations: CO_2 = carbon dioxide; IH = infantile hemangioma; Nd:YAG = neodymium-doped yttrium aluminum garnet; PDL= pulse dye laser; QoL = quality of life; RCT = randomized controlled trial

For harms, a moderate strength of evidence was noted for pigmentation changes with PDL, which was most frequently hypopigmentation. Low SOE was noted 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 (Table 36).

Table 36. Strength of evidence for harms of laser modalities

Intervention/ Outcome Study Design Quality and Number of Studies (N Total)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Finding Strength of Evidence Grade
PDL						
Pigmentation changes RCT: 1 good, 1 poor[160, 161] (173) Cohort studies: 1 good, 1 poor[162, 164] (73) Case series: 3 poor[169, 172, 173] (317)	low	Consistent	Direct	Precise	Undetected	Hypo- or hyper-pigmentation consistently reported, with hypopigmentation reported more frequently. Moderate SOE for association of PDL with skin pigmentation complications.
Bleeding RCT: 1 good[161] (121)	Low	Unknown	Direct	Imprecise	Undetected	No significant difference in bleeding between short pulse PDL and observation groups. Low SOE for association of bleeding with PDL.
Pain RCT: 1 good[161] (121)	Low	Unknown	Indirect	Imprecise	Undetected	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.
Scarring Cohort studies: 1 good[164] (50) Case series: 1 fair[175] (69)	Medium	In-consistent	Direct	Imprecise	Undetected	1/25 children receiving PDL in one study and unstated number in another had scarring. Insufficient SOE due to very small numbers of the outcome reported in studies.
Nd:YAG						
Pigmentation changes Cohort studies: 1 good[164] (50)	Low	Unknown	Direct	Imprecise	Undetected	2/25 children receiving Nd:YAG in one study had scarring. Insufficient SOE due to very small numbers of the outcome reported.

Scarring Cohort studies: 1 good, 2 poor[163, 164, 167] (386) Case series: 3 poor[176, 177, 179] (954)	Medium	Consistent	Direct	Precise	Undetected	Most studies reported scarring in ≤5% of children. Low SOE for association of scarring with Nd:YAG treatment.
Bleeding Case series: 2 poor[177, 179] (794)	High	Unknown	Direct	Precise	Undetected	Bleeding noted in 13/794 children. Insufficient SOE due to very small numbers of the outcome reported in studies.

Abbreviations: n = number; NA = not applicable; Nd:YAG = neodymium yttrium aluminium garnet; QoL = quality of life; PDL = pulse dye laser; RCT = randomized, controlled trial; SOE = strength of evidence

Effectiveness and Harms of Surgical Treatment

No comparative studies addressed surgical approaches. 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 did not consider them for effectiveness data due to the study design. Frequently reported harms included scarring and wound dehiscence. SOE was insufficient for the association of surgical approaches with harms given the small numbers of harms reported.

Findings in Relation to What is Already Known

We identified ten recent (2010-present) systematic review or meta-analyses assessing interventions for IH.[195-204] Most reviews addressed propranolol or beta-blockers: three addressed propranolol generally;[200, 201, 204] two examined effectiveness specifically for airway IH;[202, 203] one for periocular IH;[205] and two compared beta-blockers and steroids.[195, 196] One Cochrane review assessed multiple interventions,[199] and two additional reviews examined intralesional steroids[198] and laser treatment.[197]

Across reviews, investigators commented on small sample sizes, disparate outcome measures, and typically low to moderate quality studies. Most reviews noted the promise of propranolol for reducing IH lesion size but also a need for additional, larger studies with longer term followup. Overall, our findings related to the effectiveness of propranolol in most children and limited effectiveness of steroids for cutaneous IH align with findings in prior reviews. One review and meta-analysis of 10 comparative studies (six considered high quality, four of moderate quality) of children with cutaneous IH meta-analyzed data related to adverse events and reported no differences in the rate of adverse events between propranolol and corticosteroids (18 events in propranolol studies and 19 in steroid, p=0.73, 95% CI: 0.56 to 1.50).[195]

Only one prior review addressed laser treatments (two IH studies) and concluded that, despite favorable results, the evidence is weak to support the use of lasers in IH treatment (level 3b on the Oxford Centre of Evidence-based Medicine scale).[197]

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 study included individuals between 1 month and 43 years of age, with a mean age of 2 years and 11 months.[168]

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 these 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. Children were treated with a variety of beta-blockers including propranolol at various doses and administrations (oral, intralesional, or topical), timolol (topical), 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.[71, 76]

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. All comparative studies evaluated laser treatments including short-pulse and long-pulse PDL, Nd:YAG, and argon. Applicability of many of these studies is limited by historical changes in care and technology. 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 where such treatments are readily available. Further, 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. Appendix G contains full applicability tables.

Implications for Clinical and Policy Decisionmaking

This review provides evidence for use in clinical care of children who present with IH. It particularly demonstrates that there are moderate benefits with steroid treatment and significantly 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 rates of 95% for oral propranolol and 64% for topical timolol, compared with 2% for observation/placebo arms).

Steroids were associated with mean expected clearance rates of 29 percent for oral steroids and 53 percent for intralesional triamcinolone in our meta-analysis, but side effects are clinically 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 typically examines children with problematic or complicated IH and thus may not apply to all children, particularly those with minor IH. 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).[71] In addition, studies typically reported outcomes only in the short term (generally ≤12 months followup); thus, our understanding of the longer 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.

Limited research is available to guide decision-making about the use of lasers 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, however, has largely relegated laser treatment to secondary management. There is no comparative data between lasers and beta-blockers, but 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.

The literature identified to answer contextual questions 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 may support referral for patients with uncomplicated lesions in highly visible areas on a case-by-case basis.

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.

Limitations of the Comparative Effectiveness Review Process

We included studies published in English only. In our scan of the non-English language literature published since 1982 and located via our MEDLINE search, we determined that the majority would not meet our review criteria. Given the high percentage of non-eligible items in this scan, we feel that excluding non-English studies did not introduce significant bias into the review. We also required that studies reporting on "second-line" treatments such as imiquimod, bleomycin, or alpha interferon address such treatments after a trial of beta-blockers or corticosteroids, and we did not identify any such studies.

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 lack of long-term followup and analyses to explore differences in response among subgroups. Few comparative studies addressed steroids, and indications for steroid treatment compared with beta-blockers are unclear. No 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, VAS, HAS) make combining outcomes challenging.

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.

Research Gaps and Areas for Future Research

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. Future studies should use imaging modalities at the same point in the IH course to allow direct comparison.
- **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 cosmetically displeasing, 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, cosmetic issues are likely a cause for referral.
- **Appropriate dosing for propranolol and timing of treatment.** The largest RCT to date[71] 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[81] 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 are not well-understood in the population of very young children receiving beta-blockers for 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,[13, 72, 73, 77, 78, 81-83, 113, 114, 117] 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.

- **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;[57] 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 is needed. Similarly, steroids may be best used in children in the involution stage to clear residual markings or in children with threatening airway lesions, but 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 would improve our ability to combine outcomes across studies.

Conclusions

Corticosteroids demonstrate some effectiveness at reducing IH size/volume, but may be associated with clinically important 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: 86% to 100%), followed by timolol (64%, 95% BCI: 31% to 90%) and triamcinolone (53%, 95% BCI: 14% to 97%). The mean rate was 29 percent for oral steroids. 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. No 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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Abbreviations and Acronyms Used in This Report

AHRQ	Agency for Healthcare Quality Research
BCI	Bayesian Credible Interval
CER	Comparative Effectiveness Review
CI	Confidence Interval
cm	Centimeters
CO_2	Carbon Dioxide
CT	Computed Tomography
CQ	Contextual Questions
EPC	Evidence-based Practice Center
G	Group
HAS	Hemangioma Activity Score
HR	Hazard Ratio
IH	Infantile Hemangioma
IQR	Interquartile Range
IV	Intravenous
kg	Kilograms
KQ	Key Questions
LPDL	Long-pulse dye Laser
LUMBAR	Lower-body hemangioma and other cutaneous defects, Urogenital anomalies, Ulceration, Myelopathy, Bony deformities, Anorectal malformations, Arterial anomalies, and Renal anomalies
mg	Milligrams
mL	Milliliters
Mm	Millimeters
MRI	Magnetic Resonance Imaging
n	Number
NA	Not Applicable
Nd:YAG	Neodymium Yttrium Aluminum Garnet
NR	Not Reported
NS	Not Significant
OR	Odds ratio
OSD	Occult Spinal Dysraphism
PDL	Pulsed Dye Laser
PELVIS	Perineal hemangioma, External genitalia malformations, Lipomyelomeningocele, Vesicorenal abnormalities, Imperforate anus, and Skin tag
PHACES	Posterior fossa malformations, Hemangiomas, Arterial anomalies, Cardiac defects, Eye abnormalities, Sternal cleft and supraumbilical raphe
PICOTS	Population, Interventions, Outcomes, Timing, and Setting
QoL	Quality of Life
RCT	Randomized, Controlled Trial
SD	Standard Deviation
SOE	Strength of Evidence
TEP	Technical Expert Panel
TSA	Total Surface Area
US	Ultrasound
VAS	Visual Analog Scale