Effective Health Care Program
Comparative Effectiveness Review
Number 168

Diagnosis and Management of Infantile Hemangioma
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.

If you have 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, 5600 Fishers Lane, Rockville, MD 20857, or by email to epc@ahrq.hhs.gov.

Richard G. Kronick, Ph.D.  
Director  
Agency for Healthcare Research and Quality  

Arlene Bierman, M.D., M.S.  
Director  
Center for Evidence and Practice Improvement  
Agency for Healthcare Research and Quality

Stephanie Chang, M.D., M.P.H.  
Director  
Evidence-based Practice Center Program  
Center for Evidence and Practice Improvement  
Agency for Healthcare Research and Quality

Christine Chang, M.D., M.P.H.  
Task Order Officer  
Center for Evidence and Practice Improvement  
Agency for Healthcare Research and Quality
Acknowledgments

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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.

Ilona J. Frieden, M.D.*
University of California
San Francisco, CA

Arin K. Greene, M.D.
Boston Children’s Hospital
Boston, MA

Karla Hall, B.S.
National Organization of Vascular Anomalies
Greensboro, NC

Marcia Hogeling, M.D.*
Phoenix Children’s Hospital
Phoenix, AZ

Anthony J. Mancini, M.D.*
Ann & Robert H. Lurie Children’s Hospital
Chicago, IL

Gresham Richter, M.D.
University of Arkansas
Fayetteville, AR

Linda Rozell-Shannon, Ph.D., M.S.
Vascular Birthmarks Foundation

*Individuals marked with an asterisk also peer reviewed the report.
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.

Denise M. Adams, M.D.*
Cincinnati Children’s Medical Center
Cincinnati, OH

David Darrow, M.D.*
Children’s Hospital of The King’s Daughters
Norfolk, VA

Ilona J. Frieden, M.D.*
University of California
San Francisco, CA

Arin K. Greene, M.D.
Boston Children’s Hospital
Boston, MA

Marcia Hogeling, M.D.*
Phoenix Children’s Hospital
Phoenix, AZ

Dana Janssen, M.D.
Monroe Carell Jr. Children’s Hospital at Vanderbilt
Nashville, TN

Anthony J. Mancini, M.D.*
Ann & Robert H. Lurie Children’s Hospital
Chicago, IL

* Individuals marked with an asterisk also peer reviewed the report.
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:

Rongwei (Rochelle) Fu, Ph.D.
School of Public Health
Oregon Health and Science University
Portland, OR

Amy Jo Nopper, M.D.
University of Missouri-Kansas City
Kansas City, MO

Marco Sciveres, M.D.
IsMeTT-University of Pittsburgh Medical Center Italy
Palermo, Italy

Anne Zajicek, MD, Pharm.D.
Obstetric and Pediatric Pharmacology and Therapeutics Branch
Eunice Kennedy Shriver National Institute of Child Health and Human Development
Washington, DC
Diagnosis and Management of Infantile Hemangioma

Structured Abstract

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

Data sources. Multiple databases from 1982 to June 2015.

Review methods. We included comparative studies of interventions, case series addressing harms, and any study to address contextual questions. Two investigators independently screened studies and rated study quality. We extracted and summarized data qualitatively and quantitatively via network meta-analysis, which provides a relative ranking of anticipated effects among treatments. We also assessed strength of the evidence (SOE).

Results. Among 148 unique studies, 42 addressed effectiveness outcomes (6 good, 22 fair, and 14 poor quality), and 144 studies reported harms (14 good, 3 fair, and 127 poor quality). Two small studies reported differing findings for the sensitivity of ultrasound and effectiveness of imaging modalities. Studies of steroids assessed different agents; treated children typically had improvement in lesion size. Steroid harms frequently included Cushingoid facies, irritability/mood changes, and growth retardation. Beta-blockers typically demonstrated significantly greater effects on reducing lesion size than did control or other active comparators. In network meta-analysis, oral propranolol had the largest mean estimate of expected clearance (95%; 95% Bayesian credible interval [BCI]: 88% to 99%) relative to oral corticosteroids (43%, 95% BCI: 21%-66%) and control (6%, 95% BCI: 1%-11%). Beta-blocker harms included hypotension, hypoglycemia, bradycardia, sleep disturbances, and cold extremities. Surgical intervention studies primarily addressed variations of pulse dye laser (PDL) to manage IH size. Most studies reported a higher success rate with longer-pulse PDL compared to observation, with differing magnitude of effect. Laser treatment harms included hypopigmentation and scarring. No studies explicitly evaluated treatments following failure of beta-blockers or corticosteroids. Literature addressing contextual questions suggested that referral indications 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 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. Our review for contextual questions described a range of indications for referral and suggested support for a higher index of suspicion of extracutaneous IH in children with multiple cutaneous lesions or facial lesions in a beard distribution. Corticosteroids demonstrated moderate effectiveness at reducing IH size/volume (moderate SOE for improvement in IH with oral steroids compared with observation/placebo; low SOE for intralungal steroids versus 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 active comparators in most studies. Meta-analysis indicated high mean rates of IH clearance with oral propranolol (95%, 95% BCI: 88%-99%) and moderate rates for steroids (43% to 58%, with wide
BCI; moderate SOE for effects of propranolol compared with steroids). Beta-blockers and steroids also may cause clinically important harms (moderate SOE for association of oral propranolol with harms). Laser studies generally found PDL more effective than other lasers, but effects remain unclear (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).
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Executive Summary

Introduction

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

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

Diagnosis and Treatment Decisions

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

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

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

**Interventions**

The beta-blocker propranolol was approved by the U.S. Food and Drug Administration (FDA) for use in IH in March 201414-16 and was historically used in children for cardiac conditions and off-label to treat IH after the serendipitous discovery of its effects on IH lesions in 2008.17 Prior to this, corticosteroids were the drug of choice, but propranolol has become the typical choice for initial medical management in children without contraindications to beta-blockers. Steroids may be used in children with contraindications to beta-blockers or who do not respond to beta-blockers. Additionally, there is no clear consensus as to when alternative or adjunctive or historically used medications such as chemotherapeutic drugs are appropriate if first-line treatment is unsuccessful.18,19

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

**Scope and Key Questions**

**Scope and Uses of the Review**

This systematic review addresses the evidence for benefits and harms of commonly used treatments for children (ages 0-18 years) with IH: beta-blockers, corticosteroids, “second-line” drugs used after the failure of beta-blockers or steroids, and laser and surgical treatment. The decisional dilemmas that this review addresses are whether imaging modalities are useful both in diagnosis and for guiding treatment, and the expected comparative effectiveness (benefits and harms) of pharmacologic and surgical treatments, relative to observation or other active treatments. While pharmacologic and surgical interventions cannot be directly compared because of their inherent confounding by indication, we assess the comparative effectiveness of different options within both pharmacologic and surgical approaches.

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

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

Key Questions

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

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

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

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

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

**KQ3.** Among newborns, infants, and children up to 18 years of age with infantile hemangiomas for whom treatment with corticosteroids or beta-blockers is unsuccessful what is the comparative effectiveness of second line therapies including immunomodulators and angiotensin-converting enzyme inhibitors?
KQ4. Among newborns, infants, and children up to 18 years of age with infantile hemangiomas who have been referred for surgical intervention, what is the comparative effectiveness (benefits/ harms) of various types of surgical interventions (including laser and resection)?

Analytic Framework

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

Figure A. Analytic framework for KQ1

IH = infantile hemangioma; KQ = Key Question
IH = infantile hemangioma; KQ = Key Question; ND:YAG = Neodymium Yttrium Aluminum Garnet
Methods

Literature Search Strategy

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

Inclusion and Exclusion Criteria

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

Table A. Inclusion criteria

<table>
<thead>
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<th>Category</th>
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<tr>
<td>Study population</td>
<td>Newborns, infants, and children up to 18 years of age with infantile hemangiomas or suspected infantile hemangiomas</td>
</tr>
<tr>
<td>Publication languages</td>
<td>English only</td>
</tr>
</tbody>
</table>
| Publication year  | 1966-present (CQ 1 and 2)  
1982-present (KQ 1, 2, 3, 4) |
| Admissible evidence | Admissible designs                                                      |
|                   | Original research studies providing sufficient detail regarding methods and results to enable use and aggregation of the data and results |
|                   | Contextual Questions (CQ):     
- Systematic and non-systematic reviews, articles reporting on the history of IH diagnosis or treatment, practice guidelines, meta-analyses, RCTs, case series with at least 25 children with IH, and any comparative studies |
|                   | Comparative Effectiveness Key Questions (KQ):     
- Imaging accuracy: RCTs and any comparative studies  
- Benefits of interventions: RCTs and any comparative studies  
- Harms of interventions: RCTs, any comparative studies, and case series with at least 25 children with infantile hemangiomas |
Table A. Inclusion criteria (continued)

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<th>Category</th>
<th>Criteria</th>
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<tr>
<td>Other criteria</td>
<td>Studies must address one or more of the following:</td>
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<td></td>
<td>• Diagnostic imaging (e.g., magnetic resonance imaging, computed tomography, magnetic resonance angiography, echocardiography, ultrasound, endoscopy)</td>
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<td>• 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)</td>
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<tr>
<td></td>
<td>• Pharmacologic interventions (e.g., beta-blockers, corticosteroids, immunomodulators, immunosuppressants, angiotensin-converting enzyme inhibitors, antiangiogenic agents, antineoplastics)</td>
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<td>• Data (including harms) related to diagnostic modalities or interventions for infantile hemangiomas for the following outcomes:</td>
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<tr>
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<td>Imaging studies</td>
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<td>• Ability to identify presence, number, and extent of hemangiomas and associated structural anomalies (sensitivity and specificity)</td>
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<td>• Harms</td>
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<td>Surgical or pharmacologic intervention studies</td>
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<td>• Size / volume of hemangioma</td>
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<td></td>
<td>• Impact on vision</td>
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<td></td>
<td>• Aesthetic appearance as assessed by clinician or parent</td>
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<td></td>
<td>• Degree of ulceration</td>
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<td></td>
<td>• Quality of life</td>
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<td>• Harms</td>
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<td>Relevant outcomes must be able to be abstracted from data in the papers</td>
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<td></td>
<td>Data must be presented in the aggregate (vs. individual participant data)</td>
</tr>
</tbody>
</table>

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

**Study Selection**

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

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

**Data Extraction and Synthesis**

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

We summarized data for KQs qualitatively using summary tables where meta-analyses were not possible. We provided a narrative summary of relevant papers for CQs.
We identified sufficient data to address the effectiveness of pharmacologic interventions using quantitative meta-analysis methods. Studies were included in the meta-analysis subset provided that they satisfied the following additional inclusion criteria:

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

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

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

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

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

Strength of the Body of Evidence

Two senior investigators graded the strength of the evidence (SOE) for key intervention/outcome pairs (i.e., the final outcomes listed in Figures A-C) using methods based on the “Methods Guide for Effectiveness and Comparative Effectiveness Reviews.”25 We assessed the domains of study limitations (low, medium, high level of limitation), consistency (inconsistency not present, inconsistency present, unknown), directness (direct, indirect),
precision (precise, imprecise), and reporting bias. We did not assess SOE for contextual questions. The team reviewed the final SOE designation. The possible grades were:

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

We assessed the SOE for the KQs only.

**Applicability**

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

**Results**

**CQs**

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

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

**Comparative Effectiveness Questions**

**Article Selection and Overview**

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

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

**KQ1. Effectiveness and Harms of Imaging Modalities for IH**

Two poor quality diagnostic accuracy studies addressed imaging modalities.26,27 Studies assessed IH in different anatomic locations and reported differing findings for the sensitivity of ultrasound and effectiveness of imaging modalities depending on location or subtype. In one comparing magnetic resonance imaging (MRI) and ultrasound for imaging spinal anomalies (n=48), ultrasound had a sensitivity of 50 percent (95% CI: 18.7% to 81.3%) and specificity of 77.8 percent (95% CI: 40% to 97.2%) for identifying anomalies including tethered cords and intraspinal IH. We calculated the sensitivity of both modalities for identifying intraspinal hemangioma specifically: assuming a false positive value of 0, ultrasound had a sensitivity of 20 percent (95% CI: 3.30% to 71.19%), and the sensitivity of MRI was 100 percent (95% CI: 66.21% to 100%). In another study, ultrasound identified hepatic IH in 42 of 44 patients (sensitivity of 95%). Overall, studies were limited by the size of cohorts, lack of standard processes, and lack of direct comparison at the same time point using the various imaging modalities. We considered the SOE for all imaging modalities to be insufficient given single, small studies addressing different approaches, using weaker study designs and precluding a meta-analysis. The studies did not address harms.

**KQ2. Effectiveness and Harms of Corticosteroids and Beta-Blockers**

**Summary of Meta-Analysis Results**

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

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

The variation in treatment outcomes was high in beta-blocker studies. Thus, the potential for greater clearance was much higher in patients treated with oral propranolol, but the variability in outcomes makes it difficult to anticipate the likely outcome for a given patient. As noted, corticosteroid treatment demonstrated lower overall effectiveness.
To assess for methodologic heterogeneity, we ran additional models with only RCTs and with only good and fair quality studies. Estimates did not differ markedly when poor quality studies were removed, though BCI typically widened; thus, we report the model with poor quality studies included. To examine the possible effect of bias due to the inclusion of cohort studies, we fit the same model to RCT studies only. The resulting estimates were similar to those of the model fit to all studies, but with much wider posterior credible intervals. Since there was no obvious systematic bias due to study design, we reported the model estimates based on the entire body of evidence.

**Corticosteroids**

We identified 24 studies (three RCTs, one cohort study, and 20 case series) reporting outcomes and/or harms following corticosteroid use in children with IH. Comparative studies included a total of 239 children, and case series included 3508. We considered one RCT as good, one as fair, and one as poor quality and the cohort study as fair quality. We rated all case series as poor quality for harms reporting. Steroids studied varied in dose, type, and route of administration, and the ages of children included in comparative studies ranged widely from 1 to 72 months. IH size was reduced significantly in the oral prednisolone arm compared with intravenous methylprednisolone arm in one RCT.
More children in treatment arms than in an observation arm in another RCT comparing oral prednisolone, intralesional triamcinolone, and conservative management had at least a 50 percent reduction in lesion size. More children receiving intralesional triamcinolone than topical mometasone in a third RCT had an excellent response, but the study did not provide statistical comparisons. Lesion reduction did not differ among children receiving different doses of prednisolone or methylprednisolone in a cohort study. Of the 219 children who received steroids in three comparative studies reporting such data, 140 had a “good” or “fair” response to steroids. One study reported that 92 of 238 children who underwent observation only had complete or near complete regression of IH at a median of 2 years of followup. In our network meta-analysis, oral steroids had a mean estimated expected clearance rate of 43 percent (95% BCI: 21% to 66%) and intralesional triamcinolone had a rate of 58 percent with wide confidence boundaries (95% BCI: 22% to 93%). Overall, SOE is moderate for the effect of oral steroids on clearance rates and low SOE for intralesional steroids to have a modest (albeit larger) effect relative to control, with wide confidence bounds.

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

**Beta-Blockers**

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

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

**Propranolol Versus Observation or Placebo**

We identified four studies (two good and one fair quality RCTs and one fair quality cohort study) evaluating propranolol versus placebo or observation. Propranolol was associated with significantly greater clearance of IH compared with the control arm in all four studies. In the largest RCT, which included 456 children without problematic IH receiving up to 3 mg/kg/day of propranolol, 60 percent of children in the propranolol group had complete or near complete resolution of IH after 24 weeks of treatment compared with 4 percent in the placebo group. The recommended dose of propranolol in this IH population remains to be determined, but the
majority of studies to date have investigated the 2 mg/kg/day dosing regimen. Despite changes in lesion size in many children receiving propranolol, some children do not appear to respond to propranolol, but these children are not well-characterized to date.

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

**Propranolol Versus Other Active Modalities**

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

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

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

**Oral Propranolol Versus Other Beta-Blockers or Dosage Forms**

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

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

**Timolol Versus Placebo/Observation or Other Active Modality**

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

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

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

We did not identify any studies addressing this question.

**KQ4. Effectiveness and Harms of Surgical Interventions**

**Studies of Laser Treatment**

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

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

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

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

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

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

Studies of Surgical Treatment

Few comparative studies addressed surgical approaches. Two comparative studies addressed cryotherapy versus no treatment and intense pulsed light photothermolysis with or without sclerotherapy versus cryotherapy and reported improvements in IH but included few participants in each arm (total n = 263).

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

Discussion

Key Findings From CQs

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

Key Findings and Strength of Evidence for KQs

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

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

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

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

**Imaging**

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

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

**Corticosteroids**

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

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

**Beta-Blockers**

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

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

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

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

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

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

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

**Surgical Approaches**

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

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

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

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

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

Abbreviations: CT = computed tomography; IH = infantile hemangioma; MRI = magnetic resonance imaging; RCT = randomized controlled trial; SOE = strength of evidence
<table>
<thead>
<tr>
<th>Intervention</th>
<th>Type/Number of Studies (Total N Participants)</th>
<th>Key Outcome(s)</th>
<th>Strength of Evidence (SOE) Grade</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Steroids</strong></td>
<td>Oral steroids vs. Observation or Placebo</td>
<td>Improvement in IH</td>
<td>Moderate</td>
<td>In network meta-analysis oral steroids had a mean expected clearance rate of 43% (95% BCI: 21%-66%) compared with 6% (95% BCI: 1%-11%) for placebo/observation arms. Moderate SOE for greater effectiveness of oral steroids vs. placebo/observation given low precision and high study limitations.</td>
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<tr>
<td></td>
<td>Network meta-analysis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Intralesional Steroids vs. Observation or Placebo</td>
<td>Improvement in IH</td>
<td>Low</td>
<td>In network meta-analysis intralesional steroids had a mean expected clearance rate of 58% (95% BCI: 22%-93%) compared with 6% (95% BCI: 1%-11%) for placebo/observation arms. Low SOE for greater effectiveness of intralesional steroids vs. placebo/observation given relatively small numbers of participants contributing to this comparison and low precision.</td>
</tr>
<tr>
<td></td>
<td>Network meta-analysis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All steroids</td>
<td>RCT: 3 (138)</td>
<td>Clinically important harms (Cushingoid facies, growth retardation, mood changes /irritability, hypertension, infection)</td>
<td>Moderate</td>
<td>Comparative studies, case series, and package insert data consistently reported these adverse effects. Moderate SOE for association of steroids with clinically important harms due to high study limitations.</td>
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<tr>
<td></td>
<td>Cohort studies: 3 (179)</td>
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<tr>
<td></td>
<td>Case series: 10 (2974)</td>
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</table>
Table C. Summary of evidence in studies addressing effectiveness of pharmacologic interventions (continued)

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Type/Number of Studies (Total N Participants)</th>
<th>Key Outcome(s)</th>
<th>Strength of Evidence (SOE) Grade</th>
<th>Findings</th>
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</thead>
<tbody>
<tr>
<td><strong>Beta-Blockers</strong> (continued)</td>
<td></td>
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<tr>
<td>Beta-Blockers</td>
<td>Oral propranolol vs. Placebo or Observation</td>
<td>Improvement in IH</td>
<td>High</td>
<td>In network meta-analysis, the mean expected clearance rate for oral propranolol was 95% (95% BCI: 88%-99%) relative to 6% (95% BCI: 1%-11%) for placebo/observation arms; greater reductions in IH size in propranolol arms vs. control in all individual studies. High SOE for greater effectiveness of propranolol vs. placebo or observation based on individual comparisons and the meta-analysis.</td>
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<tr>
<td></td>
<td>Network meta-analysis</td>
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<td></td>
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<tr>
<td></td>
<td>RCT: 3 (510)</td>
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<tr>
<td></td>
<td>Cohort studies: 1 (45)</td>
<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td>Propranolol vs. Placebo or Observation</td>
<td>Rebound growth/Need for further treatment</td>
<td>Moderate</td>
<td>Fewer than 15% of children in treatment arms had rebound growth or required longer/additional treatment. Moderate SOE for low level of rebound growth/need for further treatment associated with propranolol given few studies addressing the outcome.</td>
</tr>
<tr>
<td></td>
<td>RCT: 1 (456)</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Cohort studies: 1 (45)</td>
<td></td>
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<tr>
<td></td>
<td>Propranolol vs. Steroids</td>
<td>Improvement in IH</td>
<td>Moderate</td>
<td>In head-to-head comparisons, propranolol more effective than steroids in 3 studies; 2 other studies reported no significant difference between oral or intralesional propranolol and oral or intralesional steroids. In network meta-analysis, pooling data from multiple studies, propranolol was superior to oral steroids (95% [95% BCI: 88% to 99%] clearance versus 43% [95% BCI: 21% to 66%] clearance). Moderate SOE for superiority of propranolol over steroids at achieving clearance based on combined effects from individual studies and network meta-analysis, high study limitations, and inconsistency.</td>
</tr>
<tr>
<td></td>
<td>Network meta-analysis</td>
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<tr>
<td></td>
<td>RCT: 1 (19)</td>
<td></td>
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<tr>
<td></td>
<td>Cohort studies: 4 (216)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Propranolol vs. Steroids</td>
<td>Amblyopia</td>
<td>Insufficient</td>
<td>No significant difference in level of amblyopia between oral propranolol and intralesional triamcinolone arms in one small study. Insufficient SOE due to single study with high limitations.</td>
</tr>
<tr>
<td></td>
<td>Cohort studies: 1 (43)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intervention</td>
<td>Type/Number of Studies (Total N Participants)</td>
<td>Key Outcome(s)</td>
<td>Strength of Evidence (SOE) Grade</td>
<td>Findings</td>
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<tr>
<td><strong>Beta-Blockers</strong> (continued)</td>
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<tr>
<td>Oral propranolol + prednisolone vs. Prednisolone vs. Propranolol alone RCT: 1 (30)</td>
<td>Improvement in IH</td>
<td>Insufficient</td>
<td>Significant size reductions from baseline in propranolol and combined arms (p values&lt;0.01) but not in prednisolone arm in one small study. Insufficient SOE due to single study with high limitations.</td>
<td></td>
</tr>
<tr>
<td>Oral propranolol vs. Other beta-blocker RCT: 1 (23) Cohort studies: 2 (77)</td>
<td>Improvement in IH</td>
<td>Low</td>
<td>In head-to-head comparisons, no significant differences in response between propranolol and atenolol in 2 studies; better response to nadolol vs. propranolol in one small study. Low SOE for no difference in response with propranolol, nadolol, or atenolol (systemic beta-blockers).</td>
<td></td>
</tr>
<tr>
<td>Oral propranolol vs. Intralesional bleomycin Cohort studies: 1 (20)</td>
<td>Improvement in IH</td>
<td>Insufficient</td>
<td>No difference between agents in one small study. Insufficient SOE due to single study with high limitations.</td>
<td></td>
</tr>
<tr>
<td>Topical timolol vs. Placebo or Observation Network meta-analysis RCT: 1 (41) Cohort studies: 2 (147)</td>
<td>Improvement in IH</td>
<td>Low</td>
<td>Timolol more effective than placebo or observation in three comparative studies. In network meta-analysis, the mean expected clearance rate for topical timolol was 62% (95% BCI: 39% to 83%) relative to 6% (95% BCI: 1% to 11%) for placebo or observation arms. Low SOE for effectiveness of timolol vs. placebo or observation based on medium study limitations and few studies.</td>
<td></td>
</tr>
<tr>
<td>Topical timolol vs. Topical imiquimod Cohort studies: 1 (38)</td>
<td>Improvement in IH</td>
<td>Insufficient</td>
<td>No significant differences in improvement in IH between groups. Insufficient SOE due to single study with high limitations.</td>
<td></td>
</tr>
<tr>
<td>Topical timolol vs. Timolol + PDL Cohort studies: 1 (102)</td>
<td>Improvement in IH</td>
<td>Insufficient</td>
<td>Timolol+PDL more effective than timolol alone (p=0.02) in one small study. Insufficient SOE due to single study with high limitations.</td>
<td></td>
</tr>
</tbody>
</table>
Table C. Summary of evidence in studies addressing effectiveness of pharmacologic interventions (continued)

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Type/Number of Studies (Total N Participants)</th>
<th>Key Outcome(s)</th>
<th>Strength of Evidence (SOE) Grade</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Beta-Blockers</strong></td>
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<td></td>
</tr>
<tr>
<td>(continued)</td>
<td>Topical timolol vs. PDL + Nd:YAG laser RCT: 1 (60)</td>
<td>Improvement in IH</td>
<td>Insufficient</td>
<td>Greater response to timolol among superficial IH and greater response to laser among mixed IH (p=NR). Insufficient SOE due to single study with high limitations.</td>
</tr>
<tr>
<td></td>
<td>Oral propranolol RCT: 3 (515) Cohort studies: 5 (277) Case series: 16 (1274)</td>
<td>Significant and minor harms (significant: hypotension, bradycardia, bronchospasm, hypoglycemia; minor: cold extremities, diarrhea, sleep changes)</td>
<td>Moderate</td>
<td>Rates of clinically important harms ranged from 0 to 100% across studies and from 1% to 50% for minor harms. Moderate SOE for association of propranolol with these harms based on high study limitations.</td>
</tr>
<tr>
<td></td>
<td>Topical timolol RCT: 1 (41) Cohort studies: 4 (287) Case series: 1 (25)</td>
<td>Lack of harms</td>
<td>Low</td>
<td>No harms observed with timolol in 5 comparative studies and 1 case series. Shortness of breath and insomnia observed in 1 of 30 children in one comparative study. Low SOE for lack of association of timolol with harms based on few studies.</td>
</tr>
</tbody>
</table>
Table C. Summary of evidence in studies addressing effectiveness of pharmacologic interventions (continued)

<table>
<thead>
<tr>
<th>Intervention</th>
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<tr>
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<tr>
<td>(continued)</td>
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<tr>
<td>Oral nadolol</td>
<td>Cohort studies: 1 (19)</td>
<td>Significant and minor harms (significant: hypotension, bradycardia, bronchospasm, hypoglycemia; minor: cold extremities, diarrhea, sleep changes)</td>
<td>Insufficient</td>
<td>Harms reported in 20% to 50% of children.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Insufficient SOE due to single, small study with high limitations.</td>
</tr>
<tr>
<td>Oral atenolol</td>
<td>RCT: 1 (23)</td>
<td>Significant and minor harms (significant: hypotension; minor: cold extremities, diarrhea, sleep changes)</td>
<td>Insufficient</td>
<td>Harms reported ranged from 3% to 27% in 2 small studies</td>
</tr>
<tr>
<td></td>
<td>Cohort studies: 1 (58)</td>
<td></td>
<td></td>
<td>Insufficient SOE due to high study limitations and few studies.</td>
</tr>
</tbody>
</table>

BCI = Bayesian credible interval; IH = infantile hemangioma; PDL = pulse dye laser; RCT = randomized controlled trial; SOE = strength of evidence
<table>
<thead>
<tr>
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</tr>
</thead>
</table>
| Lasers                       | Longer pulse PDL vs other laser types and protocols  
RCT: 1 (52)  
Cohort studies: 2 (212)                                             | Improvement in IH | Low                              | Resolution outcomes similar between laser types.  
Low SOE for no difference in effects on size reduction between longer pulse PDL and various other lasers given few studies, medium limitations, and inconsistent and imprecise findings.                                                                                                                                                                                                                                                                 |
| PDL vs. Observation          | RCT: 2 (143)                                                                                                   | Improvement in IH | Low                              | No significant difference in measured volume or proportion of clearance between groups; greater observer-ratings of improvement for PDL arm in one study.  
Low SOE for effectiveness of PDL vs. observation in reducing lesion size.                                                                                                                                                                                                                                                                  |
| PDL vs. Observation          | RCT: 2 (143)                                                                                                   | Quality of life   | Low                              | No significant differences in parent ratings of QoL in one study; more parents of children in PDL arm in another considered appearance improved than in observation arm.  
Low SOE for no difference between PDL treatment and observation in reducing lesion size due to lack of precision, few studies..                                                                                                                                                                                                           |
| Nd:YAG with extended cooling vs. Nd:YAG with standard cooling | Cohort studies: 1 (290)                                                                                       | Improvement in IH | Insufficient  
Improved resolution with extended cooling protocol vs. traditional in single study with medium limitations.  
Insufficient SOE given single study with medium limitations.                                                                                     |  
75% of children with tracheostomy had delayed speech vs. 0 with no tracheostomy in the laser treatment era.  
Insufficient SOE given small, single study with high limitations.                                                                                                                                                                                                                                                                       |
| Nd:YAG vs. CO₂ laser vs. Tracheostomy | Cohort studies: 1 (46)                                                                                       | Speech            | Insufficient  
Improved resolution with extended cooling protocol vs. traditional in single study with medium limitations.  
Insufficient SOE given single study with medium limitations.                                                                                     |  
75% of children with tracheostomy had delayed speech vs. 0 with no tracheostomy in the laser treatment era.  
Insufficient SOE given small, single study with high limitations.                                                                                                                                                                                                                                                                       |
<table>
<thead>
<tr>
<th>Intervention</th>
<th>Type/Number of Studies (Total N Participants)</th>
<th>Key Outcome(s)</th>
<th>Strength of Evidence (SOE) Grade</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lasers (continued)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>PDL</td>
<td>RCT: 2 (173)</td>
<td>Pigmentation changes</td>
<td>Moderate</td>
<td>Hypo- or hyper-pigmentation consistently reported, with hypopigmentation reported more frequently. Moderate SOE for association of PDL with skin pigmentation complications based on relatively few participants in studies.</td>
</tr>
<tr>
<td></td>
<td>Cohort studies: 2 (73)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Case series: 5 (1017)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PDL</td>
<td>RCT: 1 (121)</td>
<td>Bleeding</td>
<td>Low</td>
<td>No significant difference in bleeding between short pulse PDL and observation groups. Low SOE for association of bleeding with PDL based on one study with low limitations, unknown consistency, and imprecision.</td>
</tr>
<tr>
<td>PDL</td>
<td>RCT: 1 (121)</td>
<td>Pain</td>
<td>Insufficient</td>
<td>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.</td>
</tr>
<tr>
<td>PDL</td>
<td>Cohort studies: 1 (50)</td>
<td>Scarring</td>
<td>Insufficient</td>
<td>1/25 children receiving PDL in one study and 7/769 children in case series had scarring. Insufficient SOE due to few instances of the outcome reported in studies.</td>
</tr>
<tr>
<td></td>
<td>Case series: 3 (769)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nd: YAG</td>
<td>Cohort studies: 1 (50)</td>
<td>Pigmentation changes</td>
<td>Insufficient</td>
<td>2/25 children receiving Nd:YAG in one study had scarring. Insufficient SOE due to few instances of the outcome reported in studies.</td>
</tr>
<tr>
<td>Nd: YAG</td>
<td>Cohort studies: 3 (386)</td>
<td>Scarring</td>
<td>Low</td>
<td>Most studies reported scarring in ≤5% of children in 6 studies. Low SOE for association of scarring with Nd:YAG treatment due to few occurrences of the outcome reported.</td>
</tr>
<tr>
<td></td>
<td>Case series: 3 (954)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nd: YAG</td>
<td>Case series: 2 (794)</td>
<td>Bleeding</td>
<td>Insufficient</td>
<td>Bleeding noted in 13/794 children in 2 studies. Insufficient SOE due to few instances of the outcome reported in studies.</td>
</tr>
</tbody>
</table>
Table D. Summary of evidence in studies addressing effectiveness of surgical interventions (continued)

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Type/Number of Studies (Total N Participants)</th>
<th>Key Outcome(s)</th>
<th>Strength of Evidence (SOE) Grade</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgical</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cryotherapy vs. Observation</td>
<td>Comparative study: 1 (13)</td>
<td>Improvement in IH</td>
<td>Insufficient</td>
<td>76% of IH in treated arm vs. 12% in untreated resolved without scarring.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Insufficient SOE given single, small study with high limitations.</td>
</tr>
<tr>
<td>Cryotherapy vs. Observation</td>
<td>Comparative study: 1 (13)</td>
<td>Scarring</td>
<td>Insufficient</td>
<td>Scarring in 4 of 17 IH treated with cryotherapy.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Insufficient SOE due to single, small study with high limitations.</td>
</tr>
<tr>
<td>Photo-thermolysis with Intense Pulsed Light With or Without Sclerosis vs. Cryotherapy</td>
<td>Cohort studies: 1 (250)</td>
<td>Improvement in IH</td>
<td>Insufficient</td>
<td>More children had ≥50% reduction in IH size in the combined therapy arm than in other arms (p=NR).</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Insufficient SOE given single study with high limitations.</td>
</tr>
<tr>
<td>Excision or resection</td>
<td>Case series: 2 (142)</td>
<td>Scarring</td>
<td>Insufficient</td>
<td>Scarring in 11/192 children.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Insufficient SOE due to few instances of the outcome reported in studies.</td>
</tr>
<tr>
<td>Excision or resection</td>
<td>Case series: 7 (483)</td>
<td>Wound dehiscence</td>
<td>Insufficient</td>
<td>Dehiscences in 20/483 children.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Insufficient SOE due to few instances of the outcome reported in studies with high limitations.</td>
</tr>
</tbody>
</table>

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

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

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

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

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

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

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

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

**Limitations of the Evidence Base**

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

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

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

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

Implications for Clinical and Policy Decisionmaking

This review provides evidence for use in clinical care of children who present with IH. It particularly points to moderate benefits with steroid treatment and greater improvements with beta-blockers, with propranolol being the most commonly studied. When a decision to treat is made, our review provides qualitative and quantitative evidence that beta-blockers are associated with substantial improvement in IH size/volume (mean expected clearance rate of 95% for oral propranolol [95% BCI: 88% to 99%] and 62% [95% BCI: 39% to 83%] for topical timolol compared with 6% for observation/placebo arms [95% BCI: 1% to 11%]).

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

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

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

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

Research Gaps

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

- **Indications, optimal timing, and optimal modalities for imaging and diagnostic approaches.** Few studies in the literature we reviewed reported imaging or diagnostic techniques, and data on optimal approaches for each are lacking in the current research base. In general, imaging is infrequently used to differentiate accurately an IH from other vascular lesions. When a diagnosis is in question, a tissue biopsy is the most accurate method to determine the diagnosis. Future studies should use imaging modalities at the same point in the IH course to allow direct comparison. Studies should also report adverse effects of imaging, which are not addressed in the literature meeting criteria for this review.

- **Indications for treatment and treatment referral.** While it is likely that non-placebo-controlled studies reviewed here included mostly children with problematic IH (e.g., lesions that are vision-threatening or disfiguring, ulcerated lesions, airway/life-threatening lesions), studies did not always clearly report indications for treatment or referral for treatment. Children may be referred for life-, functional-, or vision-threatening reasons, but in the beta-blocker era, potential disfigurement is likely a cause for referral.

- **Appropriate dosing for propranolol and timing of treatment.** The largest RCT to date 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 as well as effects on cognition, memory, and the central nervous system are not well-understood in the population of very young children receiving beta-blockers for IH.

- **Treatment choice for specific lesion types and locations.** Characteristics, such as lesion size, location, and persistence, as well as modifiers such as patient age, functional impact, and IH subtype influence whether children are treated with pharmacologic agents or
surgically. Lesion characteristics also influence the choice of specific pharmacologic agents. Most studies included multiple lesion types and in multiple locations, and few included specific modifier analyses or reported outcomes by lesion characteristics. Research to improve understanding of which lesions are likely to respond best to specific agents is critical, especially as understanding of the effectiveness of beta-blockers in the involution phase is limited. Optimal treatment in the proliferative phase may be key to maximal resolution of IH.

- **Assessment of methods for assessing rebound growth.** A number of studies reported regrowth of lesions but typically did not indicate what constituted rebound growth. Greater clarity in reporting this outcome would help to clarify our understanding of effectiveness.

- **Characteristics that may influence response to beta-blockers.** Studies of beta-blockers were typically not powered to provide information on subgroups, but a percentage of children did not respond or responded minimally to propranolol. In 10 comparative studies of beta-blockers reporting these data,\(^{15,29,31-39}\) 20 percent of children (n=63/314) had a limited or no response to the agent. We lack data to assess whether improvement in lesions or promotion of involution is affected by child age or number, severity, type, or anatomic location of lesions. Similarly, understanding the mechanisms of growth of IH will promote our understanding of response to treatments and treatment safety.

- **Use of beta-blockers other than propranolol.** Small cohort studies of oral atenolol and nadolol and topical or ophthalmic timolol showed positive effects on IH resolution with few side effects. Additional RCTs of these agents, with clear reporting of lesion parameters and child characteristics, would increase our understanding of their effectiveness and comparative effectiveness versus propranolol.

- **Treatments for hepatic IH.** Few treatment studies explicitly reported if children had hepatic IH. Most studies included children with IH in multiple locations, so children could have had hepatic IH as well; however, the applicability of findings to children with visceral IH is not clear.

- **Use of steroids and laser treatments in the beta-blocker era.** Clinical practice in the United States is moving toward use of a beta-blocker as the first-line treatment for IH,\(^{40}\) however, a number of recent studies report use of steroids and laser treatments in younger children with lesions in the proliferative stage. Given the side effect profile of steroids, understanding of whether or when to use such agents in the absence of life-threatening lesions or contraindications to beta-blockers is needed. Current literature does not provide sufficient data to address these questions.

- **Interventions to follow beta-blockers or corticosteroids if such treatments fail.** We did not identify any studies that clearly reported data on this question. While most children receiving beta-blockers in the studies reviewed here responded to the medication, some had no or minimal response.

- **Standardization of scoring tools to assess change in IH.** IH outcomes are necessarily assessed using subjective measures, and investigators typically reported grading scales used to assess change in IH size or appearance. Few studies, however, commented on interrater reliability of instruments. Research to improve standardization among tools and the development of uniform scoring systems and measurements would improve our ability to combine outcomes across studies.
• **Standardization of nomenclature.** Data extraction and comparisons in the review were limited by inconsistent naming conventions. Agreement and adherence to a standard classification of lesions would improve the ability of researchers to focus on individual lesion types and determine optimal treatment regimens for specific lesions.

**Conclusions**

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


Introduction

Background

Infantile hemangiomas (IH) are the most common tumors of childhood. IH are benign but possess potential for local tissue damage, ulceration, infection, bleeding, functional impact, and pain. The International Society for the Study of Vascular Anomalies classifies IH as vascular tumors that are differentiated from vascular malformations in several ways including natural history, cellular composition, immunohistochemical expression, and pathology.\(^1\) Due to historical inconsistencies in naming conventions, it is difficult to know the true prevalence of IH, but it is estimated that they affect about 4 to 5 percent of children,\(^2\) with higher prevalence in females and Caucasians.\(^3,4\) The most common locations of IH are the head, neck, and trunk, but they can occur almost anywhere throughout the body, including the extremities, the spine, and visceral organs.\(^5-7\) 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, vescicorenal 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 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 to 5 months.\(^8,9\) With expectant observation, many patients may experience a complete or near complete involution without significant sequelae; however, IH frequently occur in cosmetically and functionally sensitive areas. Even with complete involution, some patients have permanent disfigurement and functional compromise.\(^10\) Early assessment of the extent of the hemangioma, and early, appropriate treatment of IH may potentially mitigate these complications; however, in one large multicenter treatment analysis, the first specialist visit for infants and children in the study did not occur until a mean of 5 months of age.\(^9\)

Furthermore, some lesions are particularly aggressive or morbid and can cause severe pain, ulceration, and bleeding even in early stages.\(^11,12\) 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 related 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).\(^5,7,13\)

Diagnosis and Treatment Decisions

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

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

Contraindications to specific treatments vary. Contraindications to beta-blockers include
asthma, significant bradycardia, heart block, concurrent illness such as viral gastroenteritis or
respiratory infection, history of reactive airway disease, and hypoglycemia. Contraindications
to steroids include diabetes, chronic or untreated infections, decreased bone density,
immunodeficiency, and active wound healing, and contraindications to surgical approaches
include personal or family history of adverse reactions to anesthesia.

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 disfiguring 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 when to refer patients with IH for subspecialty care.

Interventions

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

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,
potential harms of anesthesia); therefore, universal treatment is not recommended.
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 systematically reviewed and assessed the risk of bias of the literature meeting our inclusion criteria for Key Questions, which address the comparative effectiveness of interventions. We provide a narrative review of relevant literature for contextual questions as few effectiveness studies address these questions, which are related to natural history of IH and markers for occult IH.

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 Web site. Questions were as follows:

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

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

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

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

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

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

**Analytic Framework**

The analytic frameworks illustrate the population, interventions, and outcomes that guided the literature search and synthesis (Figures 1-3). 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**
IH = infantile hemangioma; KQ = Key Question

Figure 2. Analytic framework for KQ2 and KQ3

IH = infantile hemangioma; KQ = Key Question; Nd:YAG = neodymium yttrium aluminum garnet

Figure 3. Analytic framework for KQ4

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 for the Contextual Questions followed by findings of the network meta-analysis, followed by findings for each Key Question organized by intervention and outcome area where possible. Summary tables for each Key Question outline key outcomes.

The Discussion section of the report discusses the results and expands on methodologic considerations relevant to each Key Question. 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 Network Meta-Analysis
- Appendix E: Study Design Classification Algorithm
- Appendix F: Quality/Risk of Bias Ratings
- 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, to clinicians who provide care for children with IH, and for families making treatment decisions. IH is diagnosed and treated by clinicians including pediatricians, dermatologists, otolaryngologists, family physicians, nurses, nurse-practitioners, physician assistants, hematologists, and general and plastic surgeons. This report supplies practitioners and researchers up-to-date information about the current state of evidence, and assesses the quality of studies that aim to determine the outcomes and safety of treatments for IH.

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.”

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 Program Web site. 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. 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 June 2015.

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. We applied the inclusion criteria described above and in Table 1 to studies identified via our grey literature searches.

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

<table>
<thead>
<tr>
<th>Category</th>
<th>Criteria</th>
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<tbody>
<tr>
<td>Study population</td>
<td>Newborns, infants, and children up to 18 years of age with infantile hemangiomas or suspected infantile hemangiomas</td>
</tr>
<tr>
<td>Publication languages</td>
<td>English only</td>
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</tbody>
</table>
| Publication year     | 1966-present (CQ 1 and 2)  
                        | 1982-present (KQ 1, 2, 3, 4)                                                                        |
| Admissible evidence  | Admissible designs                                                                                  |
|                      | Original research studies providing sufficient detail regarding methods and results to enable use and aggregation of the data and results |
|                      | Contextual Questions (CQ):                                                                            |
|                      | • Systematic and non-systematic reviews, articles reporting on the history of IH diagnosis or treatment, practice guidelines, meta-analyses, RCTs, case series with at least 25 children with IH, and any comparative studies |
|                      | Comparative Effectiveness Key Questions (KQ):                                                          |
|                      | • Imaging accuracy: RCTs and any comparative studies                                                   |
|                      | • Benefits of interventions: RCTs and any comparative studies                                         |
|                      | • Harms of interventions: RCTs, any comparative studies, and case series with at least 25 children with infantile hemangiomas |
| Other criteria       | Studies must address one or more of the following:                                                   |
|                      | • Diagnostic imaging (e.g., magnetic resonance imaging, computed tomography, magnetic resonance angiography, echocardiography, ultrasound, endoscopy) |
|                      | • Surgical interventions (e.g., cryotherapy, resection, embolization, radiofrequency ablation therapy) or laser interventions (e.g., pulsed dye, fractionated laser, argon, carbon dioxide, neodymium (Nd): YAG, erbium) |
|                      | • Pharmacologic interventions (e.g., beta-blockers, corticosteroids, immunomodulators, immunosuppressants, angiotensin-converting enzyme inhibitors, antiangiogenic agents, antineoplastic) |
|                      | • 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)                            |

CQ = contextual question, IH = infantile hemangioma, 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 network meta-analysis subset provided that they satisfied the following additional inclusion criteria:

- Outcomes were reported quantitatively, using an objective metric for reporting intervention effects that could be converted into a proportion of IH clearance.
One or more study arms evaluated a single intervention; study arms in which two or more treatments were applied were excluded.

Reported outcomes were accompanied by an associated measure of variation or precision.

Non-control pharmacologic treatments could be reasonably classified into one of the following classes of agents: oral, intralesional, or topical propranolol; intralesional triamcinolone; topical or ophthalmic timolol; and oral steroid.

Studies evaluated IH in multiple locations (vs. specific anatomic areas) as most studies included IH in multiple areas.

In addition to the diverse suite of interventions, outcomes were reported in a variety of ways. Most identified an arbitrary threshold of IH clearance (e.g. >75%) as a positive outcome, or divided the continuous clearance measure into a small number of categories. Others reported visual analog scale scores, 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),25 the Newcastle-Ottawa Quality Assessment Scale for cohort studies,26 the QUADAS tool for diagnostic imaging studies,27 and a tool adapted from questions outlined in the RTI item bank and the McMaster McHarms tool to assess reporting of harms.28

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 rated 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” and in the updated strength of evidence guide, 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 Key Questions 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*

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<th>Grade</th>
<th>Definition</th>
</tr>
</thead>
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<td>High</td>
<td>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.</td>
</tr>
<tr>
<td>Moderate</td>
<td>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.</td>
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<tr>
<td>Low</td>
<td>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.</td>
</tr>
<tr>
<td>Insufficient</td>
<td>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.</td>
</tr>
</tbody>
</table>

* Excerpted from Berkman et al. 2014

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 provided external peer review of this report; AHRQ, a statistical expert, and an associate editor also provided comments. The draft report was posted on the AHRQ Web site for 4 weeks to elicit public comment. We addressed all reviewer comments, revised the text as appropriate, and documented 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 our network meta-analysis, which includes studies of beta-blockers and steroids. We then present results for each Key Question (comparative effectiveness questions).

We identified 966 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 68 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. 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. However, the presentation and course of IH in individual children are heterogeneous. IH usually present within the first month of life and undergo rapid 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. Many experts recommend referral at an early age (as early as 4 to 8 weeks of life) to subspecialists given this rapid proliferation.

Segmental IH are more likely to have more prolonged growth, defined as after 9 months of age. Involution typically starts by 1 year of age, but the timing of involution varies markedly. 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.40

Most lesions involute by age 5 to 7,41,42 though timing varies, and disfigurement may remain.22,38,43,44 The majority (80%) of lesions involuting after age 6 years in one series resulted in residual scarring or telangiectasia, compared with 38 percent involuting before age 6. In studies of referred populations, residual lesions (e.g., telangiectasias, atrophy, fibrofatty tissue, hypopigmentation) were reported in 25 to 69 percent of untreated IH. Lesions affecting visual cortex development may result in lasting deficits in vision even after resolution of the IH.

Indications for Treatment

The major indications for treatment of IH include risks of ulceration, disfigurement, and functional impact. 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 suggest minimal impact. Such data are often limited by the necessity to parent-report in this young population. Estimates of complications from IH vary but are generally noted to occur in approximately 30 percent of the studied population. 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. 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. Larger lesions are more likely to have complications. One study found a 5 percent increase in the likelihood of experiencing complications for every 10 cm² increase in size (OR 1.051, p<0.05). Lesions on the face and perineal regions have the highest rates of complications. Segmental lesions typically have a higher overall complication risk, though at least one study reported a lack of association with complications. 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.

Ulceration is the most common complication leading to intervention, with incidence estimated to range from 7 to 25 percent. Large size is related to increased risk of ulceration, while white discoloration to the lesion was premonitory of ulceration in one study. Ulceration may occur due to mechanical breakdown. Ulceration can occur throughout the proliferation phase, and segmental lesions and those in the anogenital, neck, or oral areas are among those at increased risk.

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. Size of periorbital lesion is predictive of amblyopia risk, and nasal location increases the disturbance risk compared to other periorbital locations.

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. For patients with cutaneous IH in the beard region, the finding of a subglottic hemangioma has been shown to increase with bilateral involvement.

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. In 17 percent of patients with known OSD, a midline lumbosacral cutaneous hemangioma was observed in another study. 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. 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 while 50 percent of children in another had treatment for the IH or associated complications including hypothyroidism or cardiac failure.

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. Larger lesions and involvement of more than one facial segment were found to be increased risk factors for PHACE. 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.
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 angiomia of lumbosacral localization]) and may require treatment of the IH to avoid functional or disfiguring sequelae.76,77

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.

The basis for the association of a greater number of cutaneous IH with hepatic IH comes primarily from case series including 453 infants with IH.71,72,78-82 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).72 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.78 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.80

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).79 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 (not clear if children were treated/untreated); lesions regressed concurrently in three children, and in two children, cutaneous lesions regressed earlier than hepatic.

In another retrospective series including 39 infants (2 weeks-6 months old at presentation), 16 had solitary hepatic IH, 23 had multiple hepatic IH, and 17 of these 23 had cutaneous IH.81 In
a series of 43 infants with IH, 27 had at least 10 cutaneous IH (median=16) and 16 had between five and nine cutaneous lesions (median=6.5). Among the nine children treated for their IH, 9 had internal IH (8 hepatic, 1 splenic), and five of the nine had more than one internal lesion. All of these children had ≥10 cutaneous IH and had no symptoms of internal IH. The study does not clearly report if any internal IH were reported among the children who did not receive treatment for cutaneous IH.

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). 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 and potential parenchymal IH. Case series have also described an association between cutaneous IH, particularly on the face, and airway IH. The finding of a subglottic IH has been shown to increase with increasing cutaneous involvement in the beard distribution. In one report including 187 children with IH on the face and neck, 16 (8.5%) had lesions with a beard distribution. 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. 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. Sixteen of these 56 (29%) had concurrent upper airway IH, also with a segmental distribution. Approximately 39 of 116 children with airway IH in another series had cutaneous IH of the head and neck, and presence of cutaneous IH was significantly associated with treatment outcomes.

Another retrospective case series assessed 342 children with IH on the upper or lower lips. 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. 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). One recent meta-analysis reported that, among 61 children with IH, nine had co-existing cutaneous lesions (number of cutaneous IH not reported).
Results of Literature Searches for Key Questions

We identified 4132 nonduplicative titles or abstracts with potential relevance, with 1273 proceeding to full text review (Figure 4). We excluded 1120 studies at full text review. We included 148 unique studies (153 publications) in the review. These 148 studies included 42 comparative studies, 38 addressing effectiveness and harms of therapies four assessing effectiveness only, and 106 case series providing data on harms only. We present findings by intervention under each Key Question.

Figure 4. Disposition of studies identified for this review

KQ = Key Question; n = number
†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 105 studies identified for KQ2, 28 addressed benefits and harms, 1 addressed only benefits, and 76 addressed only harms. Of the 41 identified for KQ4, 10 addressed benefits and harms, one addressed only benefits, and 30 addressed only harms.
*Numbers do not tally as studies could be excluded for multiple reasons.

Description of Included Studies

The 148 unique studies addressing Key Questions comprise 15 randomized controlled trials (RCTs), five prospective and 19 retrospective cohort studies, two diagnostic accuracy studies (defined as studies that compared the accuracy of imaging modalities in identifying or
characterizing infantile hemangioma [IH]), one prospective comparative study that used an untreated IH as a control, and 106 case series (used for harms data only). Most studies were conducted in Europe (n = 51) or Asia (n = 44). Forty-one were conducted in the United States or Canada and 12 in other countries including Australia, Egypt, Argentina, and Chile (Table 3). Forty-two comparative studies reported effectiveness outcomes. We considered six of these studies to be good quality, 22 fair quality, and 14 poor quality. One-hundred and forty-four studies (comparative studies and case series) reported harms/adverse events data. We considered 14 of these as good quality for harms reporting, three as fair quality for harms reporting, and the remainder (n = 127) as poor quality for harms reporting. Most studies addressed beta-blockers (n = 81, 13 of which compared a beta-blocker to another category of intervention such as corticosteroids or laser); 26 addressed lasers; 24 addressed steroids; 15 addressed surgical approaches; and two addressed diagnostic modalities.

We included 18 studies in a network meta-analysis. All studies addressed pharmacologic agents and included five RCTs and four cohort studies evaluating oral propranolol and placebo or observation or another active agent,92-100 including steroids; 96-98,100 one RCT and one cohort study comparing propranolol and other beta-blockers;101,102 three cohort studies and two RCTs assessing topical timolol compared with placebo or observation or another agent;14,103-106 and one RCT and one cohort study comparing different steroids, including oral prednisone and intralesional triamcinolone.107,108 Four studies were good quality92,98,104,107; nine were fair quality14,93,94,96,97,99,100,102,105; and five were poor quality.95,101,103,106,108 Studies in the meta-analysis included a total of 1265 children with IH.
Table 3. Characteristics of included studies addressing effectiveness and harms

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>RCTs</th>
<th>Prospective Cohort Studies†</th>
<th>Retrospective Cohort Studies</th>
<th>Diagnostic Studies</th>
<th>Case Series*</th>
<th>Total Literature</th>
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<td>Population Characteristics</td>
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</table>

MRI = magnetic resonance imaging; n = number; RCT = randomized, controlled trial
*Case series reported other outcomes; however, we only extracted harms data from case series for this review.
**Studies (n=13) 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.
†One study included in the prospective cohort column compared an IH treated with cryotherapy to an untreated IH.
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 assessing varied outcomes.
- 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\(^6^8\) and one retrospective\(^7^0\)—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 than 18 years old with IH in the lumbosacral area measuring greater than 2.5 cm.\(^6^8\) 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.\(^7^0\)

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

In one prospective cohort study, 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.\(^6^8\) 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%).

In a retrospective cohort study, ultrasound was commonly used as the first imaging 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. Given the small number of studies and heterogeneity of interventions and outcomes, we considered SOE to be insufficient for all outcomes.

**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 network meta-analysis are available in Appendix D. Effect measures (Table 4) reflect effects on the logit scale and are not immediately clinically interpretable, but they demonstrate the nominal superiority of beta-blockers. Specifically, oral propranolol had the highest estimated effect size, though there is overlap among the credible intervals of the estimates. The estimated additive effect of intralesional delivery for propranolol was -6.9 (95% Bayesian credible interval [BCI]: -11.9 to -2.5).

<table>
<thead>
<tr>
<th>Agent</th>
<th>Mean</th>
<th>Standard Error</th>
<th>95% Credible Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral propranolol</td>
<td>6.0</td>
<td>0.7</td>
<td>[4.7, 7.5]</td>
</tr>
<tr>
<td>Topical timolol</td>
<td>3.5</td>
<td>0.5</td>
<td>[2.4, 4.6]</td>
</tr>
<tr>
<td>Intralesional triamcinolone</td>
<td>3.3</td>
<td>0.8</td>
<td>[1.7, 4.9]</td>
</tr>
<tr>
<td>Oral steroid</td>
<td>2.6</td>
<td>0.5</td>
<td>[1.8, 3.6]</td>
</tr>
</tbody>
</table>

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 6 percent (95% BCI: 1% to 11%), i.e., we would expect to see, on average, 6 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.

The largest mean estimate of clearance was for oral propranolol (95%, 95% BCI: 88% to 99%). Clearance associated with the use of oral steroids was 43% (95% BCI: 21% to 66%), thus providing a clearance rate intermediate to control and use of beta-blockers. Triamcinolone, an intralesional injectable steroid, had a higher clearance rate than oral steroids, with wide BCI (58%; 95% BCI: 22% to 99%). Few data were available for intralesional propranolol, which is reflected in its larger credible interval (estimated clearance: 9%, 95% BCI: 0 to 45%).

With fairly wide confidence bounds and limited data in some areas, the relative differences among estimates are of greater importance than absolute effects in interpreting these results. The estimates provide a relative ranking of anticipated rates of lesion clearance among treatment options. Families and clinicians making treatment decisions should also factor in elements such
as lesion size, location, type, and number, which may affect choice of treatment modality, as well as patient/family preferences.

**Figure 5. Estimates of expected IH clearance**

![Graph showing expected IH clearance](image)

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. Oral propranolol was estimated to have the largest variability in clearance rate with some patients experiencing much greater clearance than others ($\sigma=2.5$, 95% BCI: 2.1 to 2.9) with timolol ($\sigma=1.5$, 95% BCI: 1.4 to 1.6), intrallesional triamcinolone ($\sigma=1.8$, 95% BCI: 1.3 to 2.3), and oral steroids ($\sigma=1.3$, 95% BCI: 1.1 to 1.6) yielding similar, lower estimates. All of the estimates of effect standard deviation were at least nominally higher than the control standard deviation, which may be a reflection of the heterogeneity of the study population in terms of response of IH to treatment.

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 1.8 (1.1 to 2.6) estimated as the pooled variance.

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

**Figure 6. Estimates of the variation of each treatment**

![Graph showing standard deviation of effects for different treatments]

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 43 percent (95% Bayesian credible interval [BCI]: 21% to 66%), and the rate for intralesional triamcinolone was 58 percent (95% BCI: 22% to 93%) compared with 6 percent (95% BCI: 1% to 11%) 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, 43 percent clearance of IH in children receiving oral steroids relative to 6 percent with placebo or no treatment.

- 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 24 studies (three RCTs, one cohort study, and 20 case series) reporting outcomes and/or harms following corticosteroid use in children with IH.40,107-129 One RCT and one case series120,122 likely report on a subset of the same children; however, the extent of overlap is not clear. Three RCTs107,108,122 and one retrospective cohort study40 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,122 Canada,107 Pakistan,108 and Turkey.40 Two studies included children with cutaneous IH, and IH types across all studies included superficial, deep, and mixed.

Comparative studies and case series assessed oral methylprednisolone, oral prednisolone, intravenous methylprednisolone, topical mometasone furoate, topical betamethasone, topical clobetasol, topical halobetasol, intralesional betamethasone, and intralesional triamcinolone acetonide and compared one agent to another or various doses of agents. One RCT included an observational/conservative control group.108 Only one RCT explicitly noted that assessors were blinded to treatment status.107 Treatment duration (where clearly reported) in comparative studies ranged from 3 weeks to 12 months. We rated one RCT as good,107 one as fair,122 and one as poor108 quality and the cohort study40 as fair quality for effectiveness outcomes. We considered the cohort study and one RCT40,122 as poor quality for harms reporting and two RCTs as good quality for harms reporting.107,108

In our network meta-analysis, oral steroids had a mean estimated expected clearance rate of 43 percent (95% BCI: 21% to 66%). Intralesional triamcinolone had a rate of 58 percent but with wide confidence bounds (95% BCI: 22% to 93%). 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 two RCTs98,100 and five cohort studies96,97,130-133 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.,97,98 Canada,96 India,100, the Netherlands,131Germany,132,133 and Egypt130 and included 308 children with IH (age range=1 to more than 9 months). We rated these studies as good98 and poor96,97,100,130-133 quality for harms reporting.

Twenty case series provided harms data on corticosteroids.109-121,123-129 Children in case series (n=3508) ranged in age from 0 to 19 years and typically had IH in multiple anatomic sites. Nine case series were conducted in the United States, three in India, two in the U.K., two in China, and one each in Qatar, Israel, Thailand, and the Netherlands. Four studies reported on only orbital or periorbital IH.111,121,127,128 Treatment duration was frequently not reported. We rated all case series as poor quality for harms reporting.

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 Intraleional 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).\textsuperscript{107} 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) at a low dose (2 mg/kg/day on alternate days) and intraleional 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.\textsuperscript{108} 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 intraleional 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

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Comparison Groups (n)</th>
<th>Age</th>
<th>Location</th>
<th>Measures of Resolution/Response</th>
<th>Resolution Outcomes</th>
<th>Rebound Growth/Recurrence, n (%)</th>
<th>Other Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pope et al. 2007&lt;sup&gt;107&lt;/sup&gt;</td>
<td>G1: Methyl-prednisolone, 30 mg/kg infused over an hour for three days monthly (10)</td>
<td>Age, mean±SD, weeks G1: 12 ± 3 G2: 11 ± 4</td>
<td>G1+G2: Multiple</td>
<td>100-mm visual analog scale (0:no change, +:decrease in size, -:increase in size) Blinded assessors</td>
<td>VAS score at 3 months, median (IQR) G1: 12 (-18 to 39) G2: 70 (54 to 80) G1 vs. G2 p=0.002</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>G2: Prednisolone, oral 2/mg/kg/day (10)</td>
<td>Type</td>
<td>All children had mixed, superficial and deep facial IH</td>
<td></td>
<td>VAS score at 1 year, median (IQR) G1: -1.5 (-35 to 22) G2: 50 (35 to 67) G1 vs. G2 p=0.005</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jalil et al. 2006&lt;sup&gt;108&lt;/sup&gt;</td>
<td>G1: Triamcinolone 1-5 mg/kg intra-lesional (25)</td>
<td>Age, mean±SD, months (range) G1+G2+G3: 5.0 ± 2.9 (1 to 12)</td>
<td>G1+G2+G3: Multiple</td>
<td>Grade I greater than 50% reduction in size Grade II less than 50% reduction in size Grade III little or no decrease (or increase) Blinded assessment: NR</td>
<td>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</td>
<td>Rebound growth G1: 0 G2: 1 G3: 0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>G2: Prednisolone, oral 2/mg/kg/ on alternate days (25)</td>
<td>Type</td>
<td>Superficial, % G1+G2+G3: 73.3 Deep G1+G2+G3: 6.6 Combined G1+G2+G3: 20</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>G3: Observation (25)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>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</td>
<td></td>
</tr>
</tbody>
</table>

G = group; IH = infantile hemangioma; IQR = interquartile range; kg = kilogram; mm = millimeter; mg= milligram; n = number; 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).<sup>122</sup> Patients in this study likely overlap with those described in a retrospective case series,<sup>120</sup> but the extent of overlap is not clear. 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

<table>
<thead>
<tr>
<th>Author, Year Comparison Groups (n)</th>
<th>Age at Initiation, Months Type</th>
<th>Location</th>
<th>Measures of Resolution/Response</th>
<th>Resolution Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pandey et al. 2010122</td>
<td>NR</td>
<td>NR</td>
<td>• Cessation of growth, lightening of color, and flattening of surface</td>
<td><strong>Excellent</strong></td>
</tr>
<tr>
<td>G1: Mometasone furoate, topical thin film applied twice daily (52)</td>
<td>NR</td>
<td>NR</td>
<td>• Positive response in all 3 parameters=Excellent</td>
<td>G1: 26 (50)</td>
</tr>
<tr>
<td>G2: Triamcinolone acetonide, intralesional 1-2 mg/kg (47)</td>
<td>NR</td>
<td>NR</td>
<td>• Positive response in 2 parameters=Good</td>
<td>G2: 30 (63.8)</td>
</tr>
<tr>
<td><strong>Quality: Fair</strong></td>
<td></td>
<td></td>
<td>• Response in single or no parameter=Poor</td>
<td>Good</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Blinded assessment: NR</td>
<td>Poor</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><strong>Response rate, n (%)</strong></td>
<td>G1: 19 (36.5)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>G2: 15 (31.9)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>G1: 7 (13.4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>G2: 2 (4.2)</td>
</tr>
</tbody>
</table>

G = group; IH = infantile hemangioma; kg = kilogram; mg = milligram; n = number; NR = not reported

**Methyprednisolone Versus Prednisolone**

In one fair quality Turkish retrospective cohort study, 283 of 1,109 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). 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. Overall, 16 children (36%) had a good or excellent response to steroids; 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). Table 7 outlines resolution outcomes.
Table 7. Key resolution outcomes in studies comparing methylprednisolone and prednisolone

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Comparison Groups (n)</th>
<th>Quality</th>
<th>Age at Initiation, Months</th>
<th>Location</th>
<th>Methods and Measures of Resolution/ Response</th>
<th>Resolution Outcomes</th>
<th>Rebound Growth/ Recurrence, n</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>G1: Prednisolone, oral 2mg/kg/day (26)</td>
<td>Fair</td>
<td>G1: 5 (2-72) G2: 4 (2-11) G3: 6 (1-36)</td>
<td>G1+G2+ G3: multiple</td>
<td>• Change in dimension, lightening of color, and softening of texture</td>
<td>• Response graded as: Excellent: 75-100% Good: 50-75% Fair: 25-50% Poor: &lt; 25%</td>
<td>G1: 4 G2+G3: 8 G1 vs. G2+G3: p=0.045</td>
</tr>
<tr>
<td></td>
<td>G2: Methylprednisolone, oral low dose 10mg/kg/day tapered to 2 mg/kg/day (11)</td>
<td></td>
<td>G1: 11 (42.3) G2: 2 (18) G3: 4 (50)</td>
<td>Capillary, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>G3: Methylprednisolone, oral low dose 30mg/kg/day tapered to 5 mg/kg/day (8)</td>
<td></td>
<td>G1: 8 (30.8) G2: 4 (36.4) G3: 4 (50)</td>
<td>Cavernous (Deep)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Quality: Fair</td>
<td></td>
<td>G1: 7 (27) G2: 5 (45.5) G3: 0</td>
<td>Mixed</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

G = group; kg = kilogram; mg = milligram; n = number; NR = not reported; ns = not significant

Harms of Steroids

Harms Reported in Studies Included in This Review

Two comparative studies that addressed steroids explicitly defined harms and were considered good quality for harms reporting. Another RCT (good quality for harms reporting) that compared prednisolone and propranolol also predefined harms. 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, as did an RCT comparing prednisolone, triamcinolone, and conservative management. One child receiving oral prednisolone discontinued the study due to persistent vomiting. Another RCT comparing oral propranolol alone, prednisolone alone, and propranolol plus prednisolone noted significantly more complications in the steroid arms compared with propranolol alone (p values not clearly reported). Complications in the combination arm and prednisolone only arm included Cushingoid appearance (n=6/10 in combination, 5/10 in prednisolone arms) and gastrointestinal upset (n=4/10 in combination arm and 3/10 in prednisolone). One child in the prednisolone arm discontinued the study due to ulceration and infection. A final RCT reported harms using a general classification. 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.98

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.40 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.96,97 One study of intralesional triamcinolone reported that no adverse events occurred.130 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.107 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 ≤0.003). Children (>70%) in both arms in this study also experienced blood pressures ≥ the 90th percentile (>15% in either arm were ≥ 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.107 In total, seven of 330 participants receiving steroids in comparative studies discontinued treatment due to adverse events.

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

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Harm/Adverse Event</th>
<th>N Studies Reporting Harm (# Participants With Harm/Total Participants)</th>
<th>Reported Rates Across Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prednisolone 2-2.6 mg/kg/day</td>
<td>Irritability107</td>
<td>1 (3/10)</td>
<td>30%</td>
</tr>
<tr>
<td></td>
<td>Crying107</td>
<td>1 (3/10)</td>
<td>30%</td>
</tr>
<tr>
<td></td>
<td>Insomnia107</td>
<td>1 (3/10)</td>
<td>30%</td>
</tr>
<tr>
<td></td>
<td>Hyperactivity107</td>
<td>1 (2/10)</td>
<td>20%</td>
</tr>
<tr>
<td></td>
<td>Vomiting107</td>
<td>1 (2/10)</td>
<td>20%</td>
</tr>
<tr>
<td></td>
<td>Abdominal pain or gastrointestinal distress100,107</td>
<td>2 (5/20)</td>
<td>20%-30%</td>
</tr>
<tr>
<td></td>
<td>Ulceration or infection100,108</td>
<td>2 (5/35)</td>
<td>10%-16%</td>
</tr>
<tr>
<td></td>
<td>Persistent high blood pressure107</td>
<td>1 (1/10)</td>
<td>10%</td>
</tr>
<tr>
<td></td>
<td>Respiratory distress107</td>
<td>1 (1/10)</td>
<td>10%</td>
</tr>
<tr>
<td></td>
<td>Chickenpox107</td>
<td>1 (1/10)</td>
<td>10%</td>
</tr>
<tr>
<td></td>
<td>Cushingoid appearance100</td>
<td>1 (5/10)</td>
<td>50%</td>
</tr>
<tr>
<td></td>
<td>Failure to thrive100</td>
<td>1 (1/10)</td>
<td>10%</td>
</tr>
</tbody>
</table>
Table 8. Harms/adverse effects in comparative studies of steroids to treat IH (continued)

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Harm/Adverse Event</th>
<th>N Studies Reporting Harm (# Participants With Harm/Total Participants)</th>
<th>Reported Rates Across Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prednisone 2-2.8 mg/kg/day</td>
<td>Irritability or behavioral changes</td>
<td>2 (8/50)</td>
<td>6%-17%</td>
</tr>
<tr>
<td></td>
<td>Oral thrush</td>
<td>1 (2/12)</td>
<td>17%</td>
</tr>
<tr>
<td></td>
<td>Insomnia</td>
<td>1 (1/12)</td>
<td>8%</td>
</tr>
<tr>
<td></td>
<td>Hypertension</td>
<td>2 (3/50)</td>
<td>5%-8%</td>
</tr>
<tr>
<td></td>
<td>Growth failure</td>
<td>2 (4/50)</td>
<td>3%-8%</td>
</tr>
<tr>
<td></td>
<td>Cushingoid appearance</td>
<td>1 (38/38)</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td>Glucosuria</td>
<td>1 (1/38)</td>
<td>3%</td>
</tr>
<tr>
<td>IV methylprednisolone 30mg/kg</td>
<td>Irritability</td>
<td>1 (3/10)</td>
<td>30%</td>
</tr>
<tr>
<td></td>
<td>Crying</td>
<td>1 (2/10)</td>
<td>20%</td>
</tr>
<tr>
<td></td>
<td>Hyperactivity</td>
<td>1 (2/10)</td>
<td>20%</td>
</tr>
<tr>
<td></td>
<td>Vomiting</td>
<td>1 (2/10)</td>
<td>20%</td>
</tr>
<tr>
<td></td>
<td>Abdominal pain</td>
<td>1 (2/10)</td>
<td>20%</td>
</tr>
<tr>
<td></td>
<td>Insomnia</td>
<td>1 (1/10)</td>
<td>10%</td>
</tr>
<tr>
<td></td>
<td>Apathy</td>
<td>1 (1/10)</td>
<td>10%</td>
</tr>
<tr>
<td></td>
<td>Behavioral change</td>
<td>1 (1/10)</td>
<td>10%</td>
</tr>
<tr>
<td></td>
<td>Respiratory distress</td>
<td>1 (1/10)</td>
<td>10%</td>
</tr>
<tr>
<td>Intraliesional triamcinolone with or without other steroids 1-5 mg/kg</td>
<td>Pain</td>
<td>1 (47/47)</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td>Itching</td>
<td>1 (9/47)</td>
<td>19.1%</td>
</tr>
<tr>
<td></td>
<td>Bleeding</td>
<td>2 (17/76)</td>
<td>17%-31%</td>
</tr>
<tr>
<td></td>
<td>Infection</td>
<td>1 (8/47)</td>
<td>17%</td>
</tr>
<tr>
<td></td>
<td>Ulceration</td>
<td>2 (8/54)</td>
<td>4%-24%</td>
</tr>
<tr>
<td></td>
<td>Ulcer and depigmentation</td>
<td>1 (1/25)</td>
<td>4%</td>
</tr>
<tr>
<td></td>
<td>Cushingoid appearance</td>
<td>1 (1/47)</td>
<td>2.1%</td>
</tr>
<tr>
<td></td>
<td>Skin atrophy</td>
<td>2 (5/72)</td>
<td>4%-8.5%</td>
</tr>
<tr>
<td></td>
<td>Skin depigmentation or hypopigmentation</td>
<td>2 (6/72)</td>
<td>6.4%-12%</td>
</tr>
<tr>
<td>Oral corticosteroids (undefined)</td>
<td>Cushingoid appearance</td>
<td>1 (42/42)</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td>Gastroesophageal reflux</td>
<td>1 (4/42)</td>
<td>10%</td>
</tr>
<tr>
<td></td>
<td>Arterial bleed</td>
<td>1 (4/42)</td>
<td>10%</td>
</tr>
<tr>
<td></td>
<td>Hirsutism</td>
<td>1 (4/42)</td>
<td>10%</td>
</tr>
<tr>
<td></td>
<td>Growth retardation</td>
<td>1 (4/42)</td>
<td>10%</td>
</tr>
<tr>
<td></td>
<td>Hypercholesterolemia</td>
<td>1 (4/42)</td>
<td>10%</td>
</tr>
<tr>
<td></td>
<td>Scarring and lip contraction</td>
<td>1 (4/42)</td>
<td>10%</td>
</tr>
<tr>
<td></td>
<td>Hypertension</td>
<td>1 (2/42)</td>
<td>5%</td>
</tr>
<tr>
<td>Mometasone furoate (topical)</td>
<td>Itching</td>
<td>1 (10/52)</td>
<td>19.2%</td>
</tr>
<tr>
<td></td>
<td>Hypopigmentation</td>
<td>1 (4/52)</td>
<td>7.7%</td>
</tr>
<tr>
<td>Observation</td>
<td>Spontaneous ulceration</td>
<td>1 (4/25)</td>
<td>16%</td>
</tr>
</tbody>
</table>

IH = infantile hemangioma; n = number

Note: One study 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. One cohort study comparing propranolol and prednisone was reported in 2 publications132,133 we use the harms data reported in the 2008 publication.133

Case series included 3508 children receiving intraliesional, oral, or topical steroids or combinations of agents, with doses of oral steroids ranging from 1 to 5 mg/kg/day and intraliesional 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 12 studies), diminished height or weight gain or growth retardation (0.45%-47% of
children in 8 studies), skin atrophy (0.95%-17% of children in five studies), hypopigmentation (1.4% to 16% of children in 6 studies), hypertension (0.11% to 5% of children in five studies), infection (2% to 15% of children in 5 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).

One study reported on several “ultrapotent” topical steroids (betamethasone dipropionate, clobetasol propionate, halobetasol propionate, 0.05%) in children with primarily superficial IH and noted that 2 of 34 children (agents received not specified) experienced hypopigmentation.127 Another reporting on several corticosteroids including oral prednisolone, clobetasol propionate, and intralesional triamcinolone plus betamethasone in 30 children with complicated IH reported adverse effects in the aggregate rather than by agent.129 Most children received prednisolone, and harms included decreased rate of linear growth (n=14), decreased weight gain (n=9), Cushingoid facies (n=7), increased weight gain (n=5), decreased head growth (n=4), hirsutism (n=4), delayed motor milestones (n=3), thrush (n=3), premature thelarche (n=2), increased rate of linear growth (n=1), sterid acne (n=1), gastritis (n=1), and varicella infection (n=1).129 Three case series evaluating intralesional steroids reported that no adverse events occurred,123,126,128 and none explicitly reported discontinuation of treatment due to adverse events.

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

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Harm/Adverse Event</th>
<th>Number Of Studies (# Participants With Harm/Total Participants)</th>
<th>Reported Rates Across Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intralesional triamcinolone+betamethasone†</td>
<td>Cushingoid appearance10,112</td>
<td>2 (5/100)</td>
<td>3%-10%</td>
</tr>
<tr>
<td></td>
<td>Hypopigmentation110</td>
<td>1 (2/70)</td>
<td>3%</td>
</tr>
<tr>
<td></td>
<td>Periocular calcification121</td>
<td>1 (1/34)</td>
<td>3%</td>
</tr>
<tr>
<td>Intralesional triamcinolone+dexamethasone</td>
<td>Abscess at injection site111</td>
<td>1 (1/27)</td>
<td>4%</td>
</tr>
<tr>
<td></td>
<td>Subcutaneous fat atrophy111</td>
<td>1 (1/27)</td>
<td>4%</td>
</tr>
<tr>
<td>Intralesional triamcinolone+prednisolone</td>
<td>Ulceration120</td>
<td>1 (130/628)</td>
<td>21%</td>
</tr>
<tr>
<td></td>
<td>Skin atrophy120</td>
<td>1 (106/628)</td>
<td>17%</td>
</tr>
<tr>
<td></td>
<td>Hypopigmentation120</td>
<td>1 (101/628)</td>
<td>16%</td>
</tr>
<tr>
<td></td>
<td>Infection120</td>
<td>1 (91/628)</td>
<td>14%</td>
</tr>
<tr>
<td></td>
<td>Cushingoid appearance120</td>
<td>1 (37/628)</td>
<td>8%</td>
</tr>
<tr>
<td></td>
<td>Growth retardation120</td>
<td>1 (37/628)</td>
<td>8%</td>
</tr>
<tr>
<td></td>
<td>Hypertension120</td>
<td>1 (30/628)</td>
<td>5%</td>
</tr>
<tr>
<td>Intralesional triamcinolone</td>
<td>Ulceration114,120</td>
<td>2 (150/1046)</td>
<td>4%-16%</td>
</tr>
<tr>
<td></td>
<td>Infection109,120</td>
<td>2 (105/991)</td>
<td>2%-12%</td>
</tr>
<tr>
<td></td>
<td>Anaphylactic shock115</td>
<td>1 (3/155)</td>
<td>2%</td>
</tr>
<tr>
<td></td>
<td>Hypopigmentation114,120</td>
<td>2 (93/1046)</td>
<td>1%-10%</td>
</tr>
<tr>
<td></td>
<td>Peptic ulcer114</td>
<td>1 (2/160)</td>
<td>1%</td>
</tr>
<tr>
<td></td>
<td>Skin atrophy109,115,120</td>
<td>3 (106/1146)</td>
<td>0.95%-11%</td>
</tr>
<tr>
<td></td>
<td>Entropia114</td>
<td>1 (1/160)</td>
<td>0.63%</td>
</tr>
<tr>
<td></td>
<td>Cushingoid appearance115,120</td>
<td>2 (6/1041)</td>
<td>0.45%-1%</td>
</tr>
<tr>
<td></td>
<td>Growth retardation120</td>
<td>1 (4/886)</td>
<td>0.45%</td>
</tr>
<tr>
<td></td>
<td>Hypertension120</td>
<td>1 (1/886)</td>
<td>0.11%</td>
</tr>
<tr>
<td>Intralesional betamethasone+dexamethasone</td>
<td>Bruising at injection site124</td>
<td>1 (NR/36)</td>
<td>NR</td>
</tr>
</tbody>
</table>
Table 9. Adverse effects in case series of steroids to treat IH (continued)

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Harm/Adverse Event</th>
<th>Number Of Studies (# Participants With Harm/Total Participants)</th>
<th>Reported Rates Across Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral prednisone or prednisolone</td>
<td>Cushingoid appearance&lt;sup&gt;116&lt;/sup&gt;</td>
<td>1 (44/62)</td>
<td>71%</td>
</tr>
<tr>
<td></td>
<td>Diminished weight gain&lt;sup&gt;116&lt;/sup&gt;</td>
<td>1 (26/62)</td>
<td>42%</td>
</tr>
<tr>
<td></td>
<td>Diminished height gain&lt;sup&gt;116&lt;/sup&gt;</td>
<td>1 (22/62)</td>
<td>35%</td>
</tr>
<tr>
<td></td>
<td>Irritable and/or napped less&lt;sup&gt;116&lt;/sup&gt;</td>
<td>1 (18/62)</td>
<td>29%</td>
</tr>
<tr>
<td></td>
<td>Personality change&lt;sup&gt;116&lt;/sup&gt;</td>
<td>1 (18/62)</td>
<td>29%</td>
</tr>
<tr>
<td></td>
<td>Gastric irritation&lt;sup&gt;116&lt;/sup&gt;</td>
<td>1 (13/62)</td>
<td>21%</td>
</tr>
<tr>
<td></td>
<td>Insomnia&lt;sup&gt;116&lt;/sup&gt;</td>
<td>1 (8/62)</td>
<td>13%</td>
</tr>
<tr>
<td></td>
<td>Fungal (oral or perineal) infection&lt;sup&gt;116&lt;/sup&gt;</td>
<td>1 (4/62)</td>
<td>6%</td>
</tr>
<tr>
<td></td>
<td>Recurrent otitis media&lt;sup&gt;116&lt;/sup&gt;</td>
<td>1 (4/62)</td>
<td>6%</td>
</tr>
<tr>
<td></td>
<td>Corticosteroid myopathy&lt;sup&gt;116&lt;/sup&gt;</td>
<td>1 (1/62)</td>
<td>2%</td>
</tr>
<tr>
<td></td>
<td>Hypertension&lt;sup&gt;116&lt;/sup&gt;</td>
<td>1 (1/62)</td>
<td>2%</td>
</tr>
<tr>
<td>Oral prednisolone</td>
<td>Cushingoid appearance&lt;sup&gt;113,120&lt;/sup&gt;</td>
<td>2 (26/524)</td>
<td>4%-20%</td>
</tr>
<tr>
<td></td>
<td>Infection&lt;sup&gt;120&lt;/sup&gt;</td>
<td>1 (55/499)</td>
<td>11%</td>
</tr>
<tr>
<td></td>
<td>Growth retardation&lt;sup&gt;120&lt;/sup&gt;</td>
<td>1 (21/499)</td>
<td>4%</td>
</tr>
<tr>
<td></td>
<td>Hypertension&lt;sup&gt;120&lt;/sup&gt;</td>
<td>1 (20/499)</td>
<td>4%</td>
</tr>
<tr>
<td></td>
<td>Skin atrophy&lt;sup&gt;120&lt;/sup&gt;</td>
<td>1 (16/499)</td>
<td>3%</td>
</tr>
<tr>
<td></td>
<td>Ulceration&lt;sup&gt;120&lt;/sup&gt;</td>
<td>1 (13/499)</td>
<td>3%</td>
</tr>
<tr>
<td></td>
<td>Hypopigmentation&lt;sup&gt;120&lt;/sup&gt;</td>
<td>1 (7/499)</td>
<td>1%</td>
</tr>
<tr>
<td>Oral prednisone</td>
<td>Cushingoid appearance&lt;sup&gt;117&lt;/sup&gt;</td>
<td>1 (32/60)</td>
<td>53%</td>
</tr>
<tr>
<td></td>
<td>Behavior changes&lt;sup&gt;117&lt;/sup&gt;</td>
<td>1 (60/60)</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td>Growth retardation&lt;sup&gt;117&lt;/sup&gt;</td>
<td>2 (2/60)</td>
<td>3%</td>
</tr>
<tr>
<td></td>
<td>Osteoporosis&lt;sup&gt;117&lt;/sup&gt;</td>
<td>1 (1/60)</td>
<td>2%</td>
</tr>
</tbody>
</table>

IH = infantile hemangioma; n = number; NR = Not reported

*One study<sup>109</sup> reported “atrophy and ulceration.”

**One study of intralesional triamcinolone reported “no systemic side effects.”<sup>123</sup> Another reported unspecified complications in 3/30 children with complicated IH receiving intralesional triamcinolone.<sup>125</sup> Two other studies reported harms in the aggregate only and not by specific agent<sup>127,129</sup> and are thus not included in this table.

†Two studies reported that there were no adverse effects with intralesional triamcinolone+betamethasone in 42 children with orbital IH<sup>126</sup> or eyelid IH.<sup>128</sup>

### 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).<sup>134-139</sup> 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.<sup>134-142</sup> 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, hicups, 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. 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 from package inserts and U.S. Food and Drug Administration (FDA) approval documents in Appendix H.

Effectiveness and Harms of Beta-Blockers

Key Points

Propranolol Versus 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: 88% to 99%) compared with 6 percent (95% BCI: 1% to 11%) for placebo or observation arms (high SOE for greater effectiveness of propranolol versus 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 Versus Other Active Modalities

- In network meta-analysis, oral propranolol was associated with a mean estimate of expected clearance of IH of 95% (95% BCI: 88% to 99%) compared with a lower rate for oral steroids (43% [95% BCI: 21% to 66%]), while in head-to-head comparisons three 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 network meta-analysis conferred moderate SOE for the superiority of propranolol over steroids at achieving IH clearance.

- In one cohort study comparing the effects of intralesional steroids and oral propranolol on vision outcomes, improvement in amblyopia did not differ between agents, but fewer children receiving propranolol required additional treatments or had side effects than those receiving steroids.

- 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 of 10 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 versus historical treatments including laser and antibiotics.

Oral Propranolol Versus 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 no difference in response of IH to propranolol, nadolol, or atenolol).

Timolol Versus Placebo/Observation or Other Active Modalities

- In our network meta-analysis, topical timolol had a mean expected clearance rate of 62 percent (95% BCI: 39% to 83%) compared with 6 percent (95% BCI: 1% to 11%) for placebo or observation (low SOE for effectiveness of timolol versus 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 81 studies (nine RCTs, 14,17,92,93,98-100,102,104 16 cohort studies, 95-97,101,103,105,106,130-133,144-150 and 56 case series 16,18,151-205) 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 (e.g., laser). Comparative studies included a total of 1539 children between the ages of less than one month to 9 years. We considered four RCTs to be good quality and five as
fair quality for effectiveness outcomes and 11 cohort studies as fair quality and five as poor quality for effectiveness outcomes.

Propranolol Versus Observation or Placebo

We identified four studies (two good\textsuperscript{17,92} and one fair\textsuperscript{99} quality RCTs and one fair quality cohort study\textsuperscript{94}) evaluating propranolol versus placebo or observation. Propranolol was associated with significantly greater clearance of IH compared with the control arm in all four studies. In the largest RCT, which included 456 children without problematic IH receiving up to 3 mg/kg/day of propranolol, 60 percent of children in the propranolol group had complete or near complete resolution of IH after 24 weeks of treatment compared with 4 percent in the placebo group.\textsuperscript{92} The recommended dose of propranolol in this IH population remains to be determined, but the majority of studies to date have investigated the 2 mg/kg/day dosing regimen. Despite changes in lesion size in many children receiving propranolol, some children do not appear to respond to propranolol, but these children are not well-characterized to date.

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

Propranolol Versus Other Active Modalities

Ten studies compared propranolol to another modality including steroids, pulse dye laser (PDL), bleomycin, or historical treatments.\textsuperscript{95-98,130-133,145,149,150} Studies comparing propranolol and steroids to reduce IH size had conflicting findings. Propranolol was more effective than steroids in three studies,\textsuperscript{96,97,132,133} while two others studies did not find effectiveness differed significantly between these treatments.\textsuperscript{98,130} In network meta-analysis, pooling data from multiple studies, propranolol was superior to oral steroids (95% clearance [95% BCI: 88% to 99%]) versus 43% clearance (95% BCI: 22% to 66%). These combined effects from individual studies and meta-analysis conferred moderate SOE for superiority of propranolol over steroids at achieving clearance.

One additional retrospective cohort study assessing only vision outcomes reported no significant differences between oral propranolol and intralesional steroids in improving amblyopia, but children in the propranolol arm had a significantly shorter duration of therapy (p<0.001) and required fewer additional treatments than those receiving steroids (p=NS).\textsuperscript{131}

Another retrospective study found that PDL therapy either in conjunction with or subsequent to propranolol therapy is more effective than propranolol alone.\textsuperscript{150} Another study found the likelihood of laser treatment was lower in participants treated with propranolol than participants who did not receive the medication.\textsuperscript{149} The study that compared propranolol with bleomycin\textsuperscript{95} 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.\textsuperscript{145}
Oral Propranolol Versus Other Beta-blockers or Dosage Forms

Three small studies compared propranolol with nadolol or atenolol, and one study evaluated oral, intralesional, and topical propranolol. Atenolol and nadolol demonstrated promising effects on lesion size (no significant differences in 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 versus propranolol in one small study. We considered the SOE as low for no difference in response with propranolol, nadolol, or atenolol (systemic beta-blockers).

Timolol Versus Placebo/Observation or Other Active Modality

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

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

Harms of Beta-blockers

In addition to these comparative studies, a total of 56 case series addressed harms of beta-blockers for IH. We assessed four case series as good quality for harms reporting, one as fair quality, and 51 as poor quality. Twenty-four comparative studies also reported harms data, and we assessed four as good quality for harms reporting and the remainder as poor quality for harms reporting. 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 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). 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.

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). Fifty of 102 children (49%) receiving 1mg/kg/day for 6 months had complete or nearly complete resolution (p<0.001 versus placebo). 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.

A small pilot RCT conducted by the same investigators of the larger, multi-center RCT described above included 14 infants (<16 weeks of age) with non-problematic IH. Participants received 3 to 4 mg/kg/day of propranolol. IH thickness decreased by a mean of 44.9 percent (95% CI: 36.0 to 76.2%) in the propranolol group compared with an increase of 11.3 percent in the placebo arm.

Another good quality RCT conducted in Australia randomized 40 children 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. 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 2 mg/kg/day divided twice daily. The study compared these participants with historical controls who had not previously received therapy. 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

<table>
<thead>
<tr>
<th>Author, Year Comparison Groups (n) Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leaute-Labreze et al. 201552</td>
</tr>
<tr>
<td>G1: Propranolol, oral 3mg/kg/day for 6 months (102)</td>
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<tr>
<td>G2: Propranolol, oral 3mg/kg/day for 3 months (101)</td>
</tr>
<tr>
<td>G3: Propranolol, oral 1mg/kg/day for 6 months (103)</td>
</tr>
<tr>
<td>G4: Propranolol, oral 1mg/kg/day for 3 months (99)</td>
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<tr>
<td>G5: placebo (55)</td>
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<tr>
<td><strong>Quality:</strong> Good</td>
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<table>
<thead>
<tr>
<th>Age Type</th>
<th>Location</th>
<th>Methods and Measures of Resolution/ Response</th>
<th>Resolution Outcomes</th>
<th>Rebound Growth/ Recurrence, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, days mean±SD</strong></td>
<td></td>
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<tr>
<td>G1: 101.6 ± 31.0</td>
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<td>G2: 107.5 ± 30.1</td>
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<tr>
<td>G3: 102.6 ± 30.1</td>
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<tr>
<td>G4: 103.6 ± 33.1</td>
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<tr>
<td>G5: 103.9 ± 31.1</td>
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<td><strong>Type, n (%)</strong></td>
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<tr>
<td>Segmental</td>
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<tr>
<td>G1: 5 (5)</td>
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<td>G2: 7 (7)</td>
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<td>G3: 7 (7)</td>
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<td>G4: 4 (4)</td>
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<td>G5: 2 (4)</td>
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<tr>
<td>Localized</td>
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<td>G1: 91 (90)</td>
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<td>G2: 88 (88)</td>
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<td>G3: 90 (88)</td>
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<tr>
<td>G4: 89 (91)</td>
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<td>G5: 48 (87)</td>
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<tr>
<td>Indeterminate</td>
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<tr>
<td>G1: 5 (5)</td>
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<tr>
<td>G2: 5 (5)</td>
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<td>G3: 5 (5)</td>
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<tr>
<td>G4: 5 (5)</td>
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<tr>
<td>G5: 5 (9)</td>
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- Serial photographs and clinical assessment by blinded investigators
- 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

- Other Outcomes

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39
Table 10. Key resolution outcomes in RCTs comparing propranolol and placebo or observation (continued)

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Comparison Groups (n)</th>
<th>Quality</th>
<th>Age Type</th>
<th>Location</th>
<th>Methods and Measures of Resolution/ Response</th>
<th>Resolution Outcomes</th>
<th>Rebound Growth/ Recurrence, n (%)</th>
<th>Other Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leaute-Labreze et al. 2013</td>
<td>G1: Propranolol, oral 3-4 mg/kg/day for 1 month (7) G2: Placebo (7)</td>
<td>Fair</td>
<td>Age, weeks mean±SD</td>
<td>G1+G2: multiple</td>
<td>G1: 12.5 ± 2.1 G2: 12.4 ± 2.6</td>
<td>Change in thickness as measured by ultrasound Double-blinded assessment of change</td>
<td>Mean change in thickness, 5 [95% CI] G1: -44.9% [36-76.2] G2: +11.3% G1 vs G2: p=0.004 Percentage change in size G1: -15.8 G2: +8.9 G1 vs G2: p=0.041</td>
<td>NR</td>
</tr>
<tr>
<td>Hogeling et al. 2011</td>
<td>G1: Propranolol oral, 2mg/kg/day in 3 daily doses (19) G2: Placebo (20)</td>
<td>Good</td>
<td>Mean weeks, n</td>
<td>G1+G2: multiple</td>
<td>G1: 67 G2: 71</td>
<td>Photographs and serial hemispheric measurements of tumor volume assessed by blinded investigators</td>
<td>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</td>
<td>NR</td>
</tr>
</tbody>
</table>
Table 10. Key resolution outcomes in RCTs comparing propranolol and placebo or observation, continued

<table>
<thead>
<tr>
<th>Author, Year Comparison Groups (n) Quality</th>
<th>Age Type</th>
<th>Location</th>
<th>Methods and Measures of Resolution/Response</th>
<th>Resolution Outcomes</th>
<th>Rebound Growth/Recurrence, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sondhi et al. 2013&lt;sup&gt;94&lt;/sup&gt;</td>
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<tr>
<td>G1: Propranolol oral, 2mg/kg/day (31)</td>
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<tr>
<td>G2: No treatment, historical controls (14)</td>
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<tr>
<td><strong>Quality:</strong> Fair</td>
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</table>

- **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

- **Location:** G1+G2: multiple

- **Methods and Measures of Resolution/Response**
  - Photographs, color and size scored; degree of involution assessed by blinded investigators
  - Change score: 0 considered completely normal skin, 10 no change in IH from pre-treatment

- **Resolution Outcomes**
  - **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)

- **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)

CI = confidence interval; G = group; IH = infantile hemangioma; kg = kilogram; mg = milligram; n = number; NR = not reported; RCT = randomized, controlled trial

### Propranolol Versus Other Active Modalities

#### Oral Propranolol Versus Oral or Intrallesional Steroids

Six studies compared oral propranolol with steroids: one compared oral propranolol and oral prednisolone<sup>98</sup>, one compared oral propranolol with prednisolone and with propranolol plus prednisolone<sup>100</sup>, two compared oral propranolol and oral prednisone<sup>96,132,133</sup>, one compared oral propranolol and unspecified oral steroids<sup>97</sup> and one compared oral propranolol and intrallesional triamcinolone and betamethasone<sup>131</sup> (Table 11). A good quality RCT compared prednisolone (2 mg/kg/day) with propranolol (2 mg/kg/day) in 19 infants. <sup>98</sup> The mean change in total surface area did not differ significantly between prednisolone and prednisone (0.41 vs 0.64 mm<sup>2</sup>, 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 RCT compared three treatment regimens: propranolol (2-3mg/kg/day), prednisolone (1-4 mg/kg/day), and both agents in 30 children between 1 week and 8 months
old. Thirty percent of children with IH in the head and neck area had parotid IH, and 53 percent of lesions overall were superficial (27% mixed, 20% deep). IH reduction from baseline was greater in the propranolol alone and propranolol plus prednisolone arms compared with the prednisolone arm (p values <0.01). Size reduction in the prednisolone arm was significantly different from baseline only at the 6-month followup (p=0.008). Size reduction did not differ by lesion type in any group although time to respond was less for mixed lesions compared with superficial and deep lesions (p<0.02).

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). At all time points, 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). In another poor quality cohort study comparing oral propranolol (2mg/kg/day) and prednisone (2mg/kg/day for 2 week tapered downwards) in 60 infants, propranolol produced significantly greater size reduction than did prednisone (median 2.0 cm² vs. 3.5 cm², p=0.006). Improvements in redness, IH height, and turgor were also greater in the propranolol arm vs. 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). There were 75 infants in the propranolol group and 42 in the corticosteroid group. 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<0.01). 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.

Finally, a fair quality retrospective cohort study compared effects on amblyopia in children with periorbital or cheek IH receiving oral propranolol (up to 3 mg/kg/day) or intralesional steroids (up to 1 mL). Children receiving steroids received injections 8 weeks apart and had a significantly longer median duration of therapy compared with those receiving propranolol (median 15.9 months, interquartile range [IQR] 10.28 vs. 6.5 months, IQR 4.87, p<0.001). Improvement in amblyopia did not differ significantly between groups (no amblyopia in 61% of the steroid group and 86% of propranolol group at followup). Two children in the steroid arm and one in the propranolol group, all of whom began therapy in the proliferative phase, had no improvement in amblyopia. The study did not assess resolution outcomes.
<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Comparison Groups (n)</th>
<th>Quality</th>
<th>Age, Months Type</th>
<th>Location</th>
<th>Methods and Measures of Resolution/Response</th>
<th>Resolution Outcomes</th>
<th>Rebound Growth/Recurrence, n</th>
<th>Other Outcomes, n (%)</th>
</tr>
</thead>
</table>
| Baumann et al. 2014 | G1: Propranolol, 2mg/kg/day in 3 daily doses (11)  
G2: Prednisolone, 2mg/kg/day in two daily doses (8) | Good | Age, mean (95% CI)  
G1: 2.5 (1.7-3.4)  
G2: 4.0 (2.8-5.2) | G1+G2: multiple | • Size measured by proportional change in total surface area (TSA) by blinded assessors | 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 |
| Bertrand et al. 2011 | G1: Propranolol, oral 2.7 mg/kg/day (12)  
G2: Prednisone, oral 2.8 mg/kg/day (12) | Fair | Age, mean (range)  
G1: 3.7 (1.5-8.7)  
G2: 3.8 (1-9) | G1+G2: multiple | • Photographs rated by blinded assessors 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: 78.7 ± 22.47  
G1: 44.8 ± 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 |
<table>
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<tr>
<th>Author, Year</th>
<th>Comparison Groups</th>
<th>Age, Months</th>
<th>Location</th>
<th>Methods and Measures of Resolution/Response</th>
<th>Resolution Outcomes</th>
<th>Rebound Growth/Recurrence, n</th>
<th>Other Outcomes, n (%)</th>
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<tbody>
<tr>
<td>Price et al. 2011&lt;sup&gt;97&lt;/sup&gt;</td>
<td>G1: Propranolol, oral 2/mg/kg/day in two daily doses (68) G2: Corticosteroids, oral 2-4 mg/kg/day (42)</td>
<td>Age, mean G1: 4.9 G2: 4.5</td>
<td>G1+G2: multiple</td>
<td>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. &lt;75% clearance Blinded assessment : NR</td>
<td>≥ 75% clearance G1: 56/68 (82%) G2: 12/42 (29%) G1 vs. G2: p&lt; 0.01</td>
<td>Relapse G1: 2-6 (data not clearly reported) G2: NR</td>
<td></td>
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<tr>
<td>Author, Year</td>
<td>Comparison Groups (n)</td>
<td>Quality</td>
<td>Age, Months</td>
<td>Type</td>
<td>Location</td>
<td>Methods and Measures of Resolution/ Response</td>
<td>Resolution Outcomes</td>
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<tr>
<td>Author, Year</td>
<td>Comparison Groups (n)</td>
<td>Quality</td>
<td>Age, Months Type</td>
<td>Location</td>
<td>Methods and Measures of Resolution/Response</td>
<td>Resolution Outcomes</td>
<td>Rebound Growth/Recurrence, n (%)</td>
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</tr>
</tbody>
</table>
| Malik et al. 2013<sup>100</sup>  
G1: Propranolol, oral 2-3/mg/kg/day in two daily doses (10)  
G2: Prednisolone, oral 1-4 mg/kg/day (10)  
G3: Propranolol, oral 2-3/mg/kg/day and Prednisolone, oral 1-4 mg/kg/day (10) | Fair | Age, mean  
G1: 4.6  
G2: 5.5  
G3: 4.7 | Type, %  
Superticial G1+G2+G3: 53  
Mixed G1+G2+G3: 26.7  
Deep G1+G2+G3: 20 | G1+G2+G3: multiple | • Photographs assessed by 2 blinded assessors  
• Color and size based on Visual Analog Scale (VAS)  
• Improvement graded as:  
75-100%  
50-74%  
25-49%  
0-24% | Mean size reduction %, VAS  
G1: 89.8  
G2: 66.6  
G3: 82.6  
Color fading, VAS  
G1: -9  
G2: -8  
G3: -9 | NR |
| Rossler et al, 2012<sup>132,133</sup>  
G1: Oral propranolol, 2 mg/kg/day (30)  
G2: Oral prednisone, 2 mg/kg/day then reduced to 1 mg/kg/day (30) | Poor | Age, mean  
G1: 4.4  
G2: 2.8 | Type: NR | G1+G2: multiple | • Size measuring length and width  
• Blinded assessment: NR  
• IH score based on color, skin level, and turgor (scale 0-6) | Median size at end of therapy  
G1: 2.0 cm²  
G2: 3.5 cm²  
G1 vs G2: p=0.006  
Median score  
G1: 2  
G2: 3  
G1 vs G2: p<0.001 | G1: 5 IH  
G2: 3 IH |

CI = confidence interval; cm = centimeter; G = group; IH = infantile hemangioma; IQR = interquartile range; kg = kilogram; mg = milligram; n = number; 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)<sup>130</sup>. 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

<table>
<thead>
<tr>
<th>Author, Year Comparison Groups (n)</th>
<th>Age, Months Type</th>
<th>Methods and Measures of Resolution/ Response</th>
<th>Resolution Outcomes</th>
<th>Rebound Growth/ Recurrence Other Outcomes</th>
</tr>
</thead>
</table>
| Awadein et al. 2011<sup>130</sup> | Age, mean±SD G1: 5.9±2.7 G2: 6.1±2.9 Type NR | - 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  
- Blinded assessment: NR | Regression of IH 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) |
| G1: Propranolol, intralesional 1mg/ml (12)  
G2: Triamcinolone, intralesional 40mg/ml(10) | G1+G2: Periocular | | | |
| **Quality:** Poor | | | | |

Abbreviations: G = group; IH = infantile hemangioma; mg = milligram; ml = milliliter; n= number; NR = not reported; SD = standard deviation

### 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).<sup>150</sup> Mean hemangioma size was larger in the concurrent treatment group (41.65 cm<sup>2</sup>) than the sequential (20.1 cm<sup>2</sup>) and propranolol-only groups (18.0 cm<sup>2</sup>). 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=0.001) for those receiving concurrent therapy (mean 92.3 ± 50.9 days) or sequential 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

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Comparison Groups (n)</th>
<th>Quality</th>
<th>Age, Months</th>
<th>Location</th>
<th>Methods and Measures of Resolution/Response</th>
<th>Resolution Outcomes</th>
<th>Rebound Growth/Recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reddy et al. 2013</td>
<td>G1: Propranolol + pulsed dye laser concurrent (12) G2: Propranolol followed by pulsed dye laser (5) G3: Propranolol only (8)</td>
<td>Fair</td>
<td></td>
<td>G1+G2+G3: Large or segmental distribution facial</td>
<td>Photographs used to rate degree of clearance score by blinded physicians: 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)</td>
<td>Complete clearance G1: 6/12 (50) G2: 2/5 (40) G3: 1/8 (12.5) G1 vs.G2 vs.G3: p=0.01</td>
<td>Rebound growth NR</td>
</tr>
</tbody>
</table>

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). Participants either received daily oral propranolol for six weeks or three bleomycin injections given at 6-week intervals. 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

<table>
<thead>
<tr>
<th>Author, Year Comparison Groups (n)</th>
<th>Age, Months Type</th>
<th>Location</th>
<th>Methods and Measures of Resolution/ Response</th>
<th>Resolution Outcomes</th>
<th>Rebound Growth/ Recurrence Other Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thayal et al. 2012¹⁶⁵</td>
<td>Age NR</td>
<td>NR</td>
<td>• Regression in size of lesion 5 grades:</td>
<td>Grade I response G1: 2</td>
<td>NR</td>
</tr>
<tr>
<td>G1: Propranolol, oral 2 mg/kg/day (10)</td>
<td>Type, %</td>
<td></td>
<td>I Complete involution (&gt; 90% response)</td>
<td>G2: 1</td>
<td></td>
</tr>
<tr>
<td>G2: Bleomycin, intralesional 0.5 mg/kg (10)</td>
<td></td>
<td></td>
<td>II Reduction in size 75-90%</td>
<td>G1: 4</td>
<td></td>
</tr>
<tr>
<td>Quality: Poor</td>
<td></td>
<td></td>
<td>III Reduction 50-75%</td>
<td>G2: 5</td>
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<td></td>
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<td></td>
<td>IV Reduction 25-50%</td>
<td>Grade III response G1: 3</td>
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<td>V Reduction &lt; 25%</td>
<td>G2: 2</td>
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<td>Blinded assessment: NR</td>
<td>Grade IV response G1: 1</td>
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<td>G2: NR</td>
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</tbody>
</table>

G = group; kg = kilogram; mg = milligram; 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.¹⁴⁹ 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). 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 to 1.38).

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).¹⁴⁵ Children in the control group had received steroids (25%), PDL (1%), antibiotics (60%), and local wound care (100%). 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

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Comparison Groups (n)</th>
<th>Quality</th>
<th>Age, Months</th>
<th>Location</th>
<th>Key Outcomes, n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perkins et al. 2014</td>
<td>G1: Propranolol era 2mg/kg/day, received (25)</td>
<td>Fair</td>
<td>Age, Mean (range)</td>
<td></td>
<td>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)</td>
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<td>G2: Propranolol era, did not receive (13)</td>
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<td>G1: 4.9 (2.0-13.5)</td>
<td>G1+G2: nasal</td>
<td>• 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</td>
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<td>G3: Pre-propranolol era (20)</td>
<td></td>
<td>G2: 4.9 (2.2-14.7)</td>
<td></td>
<td>• 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</td>
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<td>G3: 4.8 (2.0-14.3)</td>
<td>G1+G2+G3: 100</td>
<td>• 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</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Type, %</td>
<td></td>
<td>• 55% of G2 (HR: 0.45) less likely to have any type of invasive treatment when compared to G1</td>
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<tr>
<td></td>
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<td></td>
<td>Superficial and subcutaneous</td>
<td></td>
<td>• Grade change assessed by two authors not involved in treatment planning or medical and surgical therapy</td>
</tr>
</tbody>
</table>

Hermans et al. 2011

| Author, Year | Comparison Groups (n) | Quality | Age, mean at start of ulceration | Location | Key Outcomes, n |
|--------------|----------------------|---------|Age, mean at start of ulceration | | Complete healing from ulceration |
| | G1: Propranolol 2.0 to 2.5/mg/kg/d in three daily doses (20) | Fair | G1: 2.3 | G1+G2: multiple | G1: 8.7 weeks |
| | G2: Historical controls (varied treatments) (20) | | G2: 2.7 | | G2: 22.4 weeks |
| | | | Type, n: | | G1 vs.G2: p<0.015 |
| | | | Superficial nodular | | • 4 (21.1%) of 19 children who completed treatment showed some regrowth and slightly increased redness after stopping propranolol but no recurrence of ulceration. |
| | | | G1: 14 | | • 1 child (unclear if one of the 4 above) restarted due to regrowth |
| | | | Superficial macular | | Blinded assessment: NR |
| | | | G1: 4 | | |
| | | | Mixed | | |
| | | | G1: 2 | | |

CI = confidence interval; G = group; HR = hazard ratio; kg = kilogram; mg = milligram; n = number; NR = not reported

**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. 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). Of the 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

<table>
<thead>
<tr>
<th>Author, Year Comparison Groups (n) Quality</th>
<th>Age, Months Type</th>
<th>Location</th>
<th>Methods and Measures of Resolution/Response</th>
<th>Resolution Outcomes</th>
<th>Rebound Growth/Recurrence, n (%)</th>
</tr>
</thead>
</table>
| Abarrzua-Araya et al. 2014102            | Age, mean±SD G1+G2: 5.2±3.5 (range: 2-14) | G1+G2: multiple | • Blinded assessment of serial photographs plus 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) |

G1: Propranolol, oral 2mg/kg/day in 3 daily doses for 6 months (10)  
G2: Atenolol, oral 1mg/kg/day single daily dose for 6 months (13)  
Quality: Fair
### Table 16. Resolution outcomes in studies comparing beta-blockers (continued)

<table>
<thead>
<tr>
<th>Author, Year Comparison Groups (n) Quality</th>
<th>Age, Months Type</th>
<th>Location</th>
<th>Methods and Measures of Resolution/Response</th>
<th>Resolution Outcomes</th>
<th>Rebound Growth/Recurrence, n (%)</th>
</tr>
</thead>
</table>
| De Graaf et al, 2013146-148 | Age, n (%) | G1+G2: multiple | • Serial photographs and clinical assessment of involution (color change, softening to palpation and reduction in size) by blinded assessors  
• 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 |
| G1: Atenolol, oral 1 mg/kg/day up to 3 mg/kg (30)  
G2: Propranolol, oral 2 mg/kg/day (historical group) (28) | 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: 2 | 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 | | |
| Quality: Fair | | | | | |

**Nadolol Versus Propranolol**

In a poor quality 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). 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

<table>
<thead>
<tr>
<th>Author, Year Comparison Groups (n) Quality</th>
<th>Age, months Type</th>
<th>Location</th>
<th>Methods and Measures of Resolution/Response</th>
<th>Resolution Outcomes</th>
<th>Rebound Growth/Recurrence, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pope et al, 2012101 G1: Nadolol suspension up to 4 mg/kg/day (10) G2: Propranolol maximum dose 2-3 mg/kg/day (historical group) (9)</td>
<td>G1: 4.1 ± 2.23 G2: 4.8 ± 1.92</td>
<td>G1+G2: multiple</td>
<td>• Serial photographs and clinical assessment using 100-mm visual analog scale (VAS); blinded assessors (-): 100% worsening 0: no change (+): 100% shrinkage where 5 mm represented 10% change</td>
<td>Percentage IH shrinkage, mean ± SD G1: 97 ± 3.05% G2: 86 ± 14.82% G1 vs. G2: p&lt; 0.008</td>
<td>NR</td>
</tr>
</tbody>
</table>

G = groups; IH = infantile hemangioma; kg = kilograms; mm = millimeter; mg = milligram; 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 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).93 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 less than 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

<table>
<thead>
<tr>
<th>Author, Year Comparison Groups (n) Quality</th>
<th>Age, Months Type</th>
<th>Location</th>
<th>Methods and Measures of Resolution/Response</th>
<th>Resolution Outcomes</th>
<th>Rebound Growth/Recurrence, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zaher et al. 201393</td>
<td></td>
<td></td>
<td>G1+G2+G3: multiple</td>
<td></td>
<td></td>
</tr>
<tr>
<td>G1: Propranolol oral, 2mg/kg/day in 2 daily doses (15)</td>
<td>Age, mean±SD (range)</td>
<td>G1: 9.13 (3-18)</td>
<td>Grading system comparing photographic documentation; unblinded assessment</td>
<td>Excellent response G1: 9 (60) G2: 3 (20) G3: 2 (13.3)</td>
<td>Rebound growth, n (%) G1: 1 (6.7) G2: 1 (6.7) G3: 2 (13.3)</td>
</tr>
<tr>
<td>G2: Propranolol, topical, 1% ointment applied twice daily (15)</td>
<td>G1: 9.13 (3-18)</td>
<td>Good: sustained plateau with ≥ 50% reduction in size</td>
<td>Good response G1: 2 (13.3) G2: 5 (33.3) G3: 3 (20)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quality: Fair</td>
<td>G3: 9.0 (3-18)</td>
<td>Poor: no response or worsening of IH</td>
<td>Poor G1: 3 (20) G2: 5 (33.3) G3: 7 (46.7)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

G = group; IH = infantile hemangioma; kg = kilogram; mg = milligram; n= number; NR = not reported; SD = standard deviation

Timolol Versus Placebo/Observation or Other Modalities

Timolol Compared With Placebo or Observation

In a good quality double-blind, placebo-controlled 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).104

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.144 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). 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

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Comparison Groups (n)</th>
<th>Quality</th>
<th>Age, Months Type</th>
<th>Location</th>
<th>Methods and Measures of Resolution/Response</th>
<th>Resolution Outcomes</th>
<th>Rebound Growth/ Recurrence, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chan et al. 2013</td>
<td>G1: Topical timolol maleate 0.5% gel (19)</td>
<td>Good</td>
<td>Age, mean±SD</td>
<td>G1+G2: multiple</td>
<td>• Serial photographs and clinical assessment volume estimation by blinded assessors</td>
<td>Infants with IH volume reduced by ≥ 5%, n (%)</td>
<td>No clinically significant rebound occurred in those successfully treated</td>
</tr>
<tr>
<td></td>
<td>G2: Placebo (22)</td>
<td></td>
<td>G1: 2.1 ± 0.8 G2: 3 ± 0.9</td>
<td></td>
<td></td>
<td>G1: 15 (60)  G2: 18 (11) G1 vs.G2: p=0.01</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Type, %: Superficial G1+G2: 100</td>
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<td></td>
<td></td>
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<td></td>
<td></td>
<td>Redness score</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No redness, n (%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>G1: 15 (47)  G2: 18 (6)</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Half red, %</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>G1: 47</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>G2: 39</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Completely red, %</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>G1: 6</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>G2: 5</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>G1 vs.G2 p= 0.003</td>
<td></td>
</tr>
<tr>
<td>Author, Year</td>
<td>Age, Months</td>
<td>Type</td>
<td>Location</td>
<td>Methods and Measures of Resolution/Response</td>
<td>Resolution Outcomes</td>
<td>Rebound Growth/Recurrence, n (%)</td>
<td></td>
</tr>
<tr>
<td>--------------</td>
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</tr>
<tr>
<td>Chambers et al. 2012</td>
<td>Age, mean±SD</td>
<td>Type, n</td>
<td>Location</td>
<td>• Photographs</td>
<td>Response to treatment, n (%)</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>G1: Timolol maleate gel 0.25% (13)</td>
<td>G1: 4.8 G2: 3.7</td>
<td>Superficial: G1: 5 G2: 4 Mixed G1: 7 G2: 5 Deep G1: 1 G2: 1</td>
<td>Periocular (100%)</td>
<td>• 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)</td>
<td>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</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yu et al. 2013</td>
<td>Age</td>
<td>Type, %</td>
<td>Location</td>
<td>• Photographs</td>
<td>Response to treatment, n (%)</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>G1: Timolol, topical, drops three times daily (101)</td>
<td>G1+G2: multiple</td>
<td>Superficial: 100</td>
<td></td>
<td>• Categorized as:</td>
<td>Class 1: ineffective Class 2: controlled growth Class 3: promoted regression • Blinded assessment: NR</td>
<td>In 12 patients with complete resolution, no regrowth noted at 3-5 month followup</td>
<td></td>
</tr>
<tr>
<td></td>
<td>G1: 1-6 months G1+G2: 88 7-12 months G1 +G2: 36</td>
<td></td>
<td></td>
<td></td>
<td>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)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

G = group; IH = infantile hemangioma; n = number; NR = not reported; SD = standard deviation

Timolol Ophthalmic Solution Versus Imiquimod Cream

One fair quality retrospective cohort study evaluated imiquimod cream versus timolol ophthalmic solution for treatment of superficial proliferating IH (Table 20). There were 40 treated IH among the participants. 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 hemangioma activity score did not differ significantly between the two groups.
Table 20. Resolution outcomes in studies comparing timolol and imiquimod

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Comparison Groups (n)</th>
<th>Quality</th>
<th>Age, Months</th>
<th>Location</th>
<th>Methods and Measures of Resolution/Response</th>
<th>Resolution Outcomes, n</th>
<th>Rebound Growth/Recurrence</th>
<th>Other Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Qiu et al. 2013</td>
<td>G1: Topical imiquimod 5% cream (20)</td>
<td>Fair</td>
<td>G1: 3.1 ± 1.20</td>
<td>G1+G2: multiple</td>
<td>• Visual analog scale (VAS) • Hemangioma Activity Score (HAS) evaluations conducted by two study investigators • Blinded assessment: NR</td>
<td>VAS and HAS results presented in figures</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td></td>
<td>G2: Topical timolol ophthalmic 0.5% solution (20)</td>
<td></td>
<td>G2: 3.0 ± 1.96</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>G1+G2: 100</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

Topical Timolol Versus Laser

One fair quality RCT conducted in Egypt compared topically applied timolol (0.5% ophthalmic solution) and sequential PDL and Nd:YAG laser in 60 children (age range not clear) with superficial or mixed IH.14 Children received treatment for roughly 4 to 5.5 months. Forty percent of children in the timolol group and 20 percent in the laser group had an excellent response (defined as improvement of 76-100%), and IH hemoglobin level declined significantly from baseline in both groups. Improvement in IH in either group did not differ between children who were greater or less than 6 months of age, but response was greater in superficial lesions compared with mixed lesions in both groups. More mixed lesions responded to laser than to timolol, with deep components of superficial lesions not responding to timolol. Superficial lesions responded more quickly and more extensively to timolol than to laser (p=NR). The study provided few statistical comparisons of timolol versus laser.

In a poor quality retrospective cohort study comparing topical timolol alone with timolol plus PDL in 102 children with superficial IH, children received treatment for between 2 and 24 months.106 Overall, 97 percent of children had improvement in IH (3 children in the timolol arm had no change, 28 had >75% improvement), with greater improvement in the combination arm compared with the timolol alone arm (mean global assessment score change of 2.66 vs. 1.88, p=0.02, score range=-1 to 4 with higher number indicating more improvement). Table 21 outlines key outcomes.
Table 21. Resolution outcomes in studies comparing timolol and laser

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Comparison Groups (n)</th>
<th>Age, Months Type</th>
<th>Location</th>
<th>Methods and Measures of Resolution/Response</th>
<th>Resolution Outcomes, n</th>
<th>Rebound Growth/Recurrence</th>
<th>Other Outcomes</th>
</tr>
</thead>
</table>
| Tawfik et al. 2015 | G1: Topical timolol ophthalmic 0.5% solution (30)  
G2: Combined sequential laser PDL (585 nm) and Nd:YAG (1064 nm) (30) | Age, n (%)  
≤ 6 months: G1: 8 (26.7)  
G2: 14 (46.7)  
> 6 months: G1: 22 (73.3)  
G2: 16 (53.3) | G1+G2: multiple | • Photographs  
• Efficacy evaluated by two blinded physicians  
• Response to treatment graded  
Excellent: 76-100% improvement  
Good: 51-75%  
Moderate: 26-50%  
Mild: < 25%  
No improvement: 0% | Response to treatment, n (%)  
Excellent: G1: 9 (30)  
G2: 3 (10)  
Good: G1: 9 (30)  
G2: 7 (23)  
Moderate: G1: 4 (13)  
G2: 9 (30)  
Mild: G1: 4 (13)  
G2: 7 (23)  
Poor | No rebound growth in either group |
| Park et al. 2014 | G1: Timolol ophthalmic 0.5% solution (61)  
G2: Combination topical timolol ophthalmic 0.5% solution plus adjunctive pulsed dye laser treatment (41) | Age, Months Type | G1+G2: multiple | • Photographs  
• Clinical evaluation of efficacy by two independent physicians  
Global assessment score (GAS)  
4: 75-100% improvement  
3: 50-74%  
2: 25-49%  
1: 0-24%  
0: 0  
-1: < 0 | Mean GAS score change  
G1: 1.88  
G2: 2.66  
G1 vs. G2: p=0.018 | % improvement, n (%)  
75-100: G1: 14 (23)  
G2: 17 (41)  
50-74: G1: 14 (23)  
G2: 12 (29)  
25-49: G1: 11 (18)  
G2: 8 (20)  
0-24: G1: 19 (31)  
G2: 4 (10)  
≤0: G1: 3 (5)  
G2: 0 | No rebound growth in either group |

G = group; GAS = global assessment score; n = number; nm = nanometer; NR = not reported
Harms of Beta-Blockers

Harms Reported in Studies Included in This Review

Thirteen comparative studies specifically defined harms of beta-blockers used to treat IH. Several studies specifically noted that no harms were observed: one study evaluating topical timolol maleate 0.5 percent gel compared to placebo; a cohort study evaluating topical 0.25 percent timolol maleate gel; one RCT of ophthalmic timolol, 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. An RCT comparing atenolol versus propranolol and two other cohort studies of intralesional propranolol and up to 2mg/kg/day of oral propranolol reported that no harms were observed. Another RCT of propranolol (3-4 mg/kg/day) including 14 participants reported asymptomatic hypotension and bradycardia in an unstated number of infants and discontinuation of treatment in one child due to drowsiness.

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). 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 another RCT comparing propranolol, prednisolone, and propranolol plus prednisolone, more children in the steroid and combination arms had adverse effects than those in the propranolol alone arm. The 10 children receiving propranolol had two side effects: one case of asymptomatic hypoglycemia, and one case of somnolence. 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. One study of topical timolol reported shortness of breath and insomnia in one of 30 children, while another reported no harms associated with topical timolol in another cohort study comparing timolol and laser.

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 reported hypotension and bradycardia in three of 15 children, and two syncopal episodes in another child. Few children receiving beta-blockers in comparative studies discontinued treatment due to adverse effects (n=24/1062, 2.3%). Studies typically included a limited number of participants and may not have been adequately powered to detect harms (Table 22).
Table 22. Harms/adverse effects in comparative studies of beta-blockers to treat IH

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Harm/Adverse Event</th>
<th>N Studies Reporting Harm (# Participants With Harm/Total Participants)</th>
<th>Reported Rates Across Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral propranolol 2-3 mg/kg/day</td>
<td>Bronchial hyperreactivity[^47]</td>
<td>1 (4/28)</td>
<td>14%</td>
</tr>
<tr>
<td></td>
<td>Bronchiolitis[^17]</td>
<td>1 (4/19)</td>
<td>21%</td>
</tr>
<tr>
<td></td>
<td>Bronchospasm[^94]</td>
<td>1 (1/31)</td>
<td>3%</td>
</tr>
<tr>
<td></td>
<td>Cold extremities[^17,131,145]</td>
<td>3 (13/53)</td>
<td>5%-43%</td>
</tr>
<tr>
<td></td>
<td>Constipation or gastrointestinal complaints[^90,145,147]</td>
<td>3 (5/60)</td>
<td>5%-11%</td>
</tr>
<tr>
<td></td>
<td>Dental caries[^17]</td>
<td>1 (1/19)</td>
<td>5%</td>
</tr>
<tr>
<td></td>
<td>Elevated alkaline[^17]</td>
<td>1 (1/19)</td>
<td>5%</td>
</tr>
<tr>
<td></td>
<td>Hypoglycemia[^97,100,147]</td>
<td>3 (4/106)</td>
<td>1%-10%</td>
</tr>
<tr>
<td></td>
<td>Hypotension[^93,96,147]</td>
<td>3 (4/55)</td>
<td>4%-20%</td>
</tr>
<tr>
<td></td>
<td>Ulceration[^17]</td>
<td>1 (1/19)</td>
<td>5%</td>
</tr>
<tr>
<td></td>
<td>Sleep disturbance (insomnia, drowsiness, restless sleep)^[^17,94,96,100,145,147]</td>
<td>6 (31/150)</td>
<td>6%-50%</td>
</tr>
<tr>
<td></td>
<td>Streptococcal infection[^17]</td>
<td>1 (1/19)</td>
<td>5%</td>
</tr>
<tr>
<td></td>
<td>Syncopal attack[^93]</td>
<td>1 (1/15)</td>
<td>7%</td>
</tr>
<tr>
<td></td>
<td>Viral gastroenteritis[^17]</td>
<td>1 (1/19)</td>
<td>5%</td>
</tr>
<tr>
<td></td>
<td>&quot;Viral upper respiratory infection[^17,97]</td>
<td>2 (2/87)</td>
<td>1%-5%</td>
</tr>
<tr>
<td></td>
<td>Poor feeding[^145]</td>
<td>1 (2/20)</td>
<td>10%</td>
</tr>
<tr>
<td></td>
<td>Fever[^97]</td>
<td>1 (2/68)</td>
<td>3%</td>
</tr>
<tr>
<td></td>
<td>Rash[^97]</td>
<td>1 (2/68)</td>
<td>3%</td>
</tr>
<tr>
<td></td>
<td>Tachycardia[^97]</td>
<td>1 (1/68)</td>
<td>1%</td>
</tr>
<tr>
<td></td>
<td>Hypotonia[^92]</td>
<td>1 (3/30)</td>
<td>10%</td>
</tr>
<tr>
<td></td>
<td>Pulmonary obstruction[^132]</td>
<td>1 (2/30)</td>
<td>6.7%</td>
</tr>
<tr>
<td>Oral propranolol 4 mg/kg/day</td>
<td>Drowsiness[^99]</td>
<td>1 (1/7)</td>
<td>14%</td>
</tr>
<tr>
<td>Oral propranolol (2.2 mg/kg/day) + prednisolone (1.6 mg)</td>
<td>Gastrointestinal upset[^100]</td>
<td>1 (4/10)</td>
<td>40%</td>
</tr>
<tr>
<td></td>
<td>Infection[^100]</td>
<td>1 (1/10)</td>
<td>10%</td>
</tr>
<tr>
<td></td>
<td>Cushingoid appearance[^100]</td>
<td>1 (6/10)</td>
<td>60%</td>
</tr>
<tr>
<td>Intralesional propranolol 1 mg</td>
<td>Pain/inconvenience of therapy[^93]</td>
<td>1 (3/15)</td>
<td>20%</td>
</tr>
<tr>
<td>Oral atenolol 3mg/kg/day</td>
<td>Hypotension[^147]</td>
<td>1 (1/30)</td>
<td>3%</td>
</tr>
<tr>
<td></td>
<td>Restless sleep[^147]</td>
<td>1 (8/30)</td>
<td>27%</td>
</tr>
<tr>
<td></td>
<td>Constipation[^147]</td>
<td>1 (2/30)</td>
<td>7%</td>
</tr>
<tr>
<td></td>
<td>Diarrhea[^147]</td>
<td>1 (2/30)</td>
<td>7%</td>
</tr>
<tr>
<td>Oral nadolol up to 4 mg/kg/day</td>
<td>Cold extremities[^101]</td>
<td>1 (2/10)</td>
<td>20%</td>
</tr>
<tr>
<td></td>
<td>Cold induced wheezing[^101]</td>
<td>1 (1/10)</td>
<td>10%</td>
</tr>
<tr>
<td></td>
<td>Sleep disturbance[^101]</td>
<td>1 (1/10)</td>
<td>10%</td>
</tr>
<tr>
<td></td>
<td>Gastrointestinal symptoms[^101]</td>
<td>1 (5/10)</td>
<td>50%</td>
</tr>
<tr>
<td>Placebo</td>
<td>Sleep disturbance[^17]</td>
<td>1 (2/20)</td>
<td>10%</td>
</tr>
<tr>
<td></td>
<td>Ulceration[^17]</td>
<td>1 (1/20)</td>
<td>5%</td>
</tr>
<tr>
<td></td>
<td>Visual compromise[^17]</td>
<td>1 (1/20)</td>
<td>5%</td>
</tr>
<tr>
<td></td>
<td>Bronchiolitis[^17]</td>
<td>1 (1/20)</td>
<td>5%</td>
</tr>
</tbody>
</table>

IH = infantile hemangioma; kg = kilogram; mg = milligram; n = number
*One study[^93] reported hypotension and bradycardia in 3/15 children.
**One study[^97] reported upper respiratory infection and reactive airway disease in 1/68 children.

The safety population in a large RCT[^92] included 456 patients in total (Table 23). 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 23. Harms/adverse events reported by dose in Leaute-Labreze et al. 2015

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

kg = kilogram; mg = milligram; n = number

Table 24 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. However, reductions in these parameters were not always clinically significant. In most prospective case series, clinically important hypotension and bradycardia were not reported; asymptomatic changes were specifically noted in several series. 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 several case series, and most studies of topical beta-blockers reported that no adverse events were observed, though studies typically did not describe methods for harms monitoring. Two studies of topical applications reported recurrent itching associated with topical propranolol in 3 percent of children and sleep disturbances in 1 percent of children receiving topical timolol. The remaining case series reported few adverse events, and those reported rarely caused discontinuation of the medication. In total, 51/3810 (1.3%) 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 24. Adverse effects in case series of propranolol to treat IH

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Harm/Adverse Event</th>
<th>Number of Studies (# Participants With Harm/Total Participants)</th>
<th>Reported Rates Across Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral Propranolol 1-1.5 mg/kg/day</td>
<td>Decrease in heart rate and blood pressure(^{171})</td>
<td>1 (89/89)</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td>Elevation of liver enzymes (ALT, AST) (^{171})</td>
<td>1 (5/89)</td>
<td>6%</td>
</tr>
<tr>
<td></td>
<td>Hypoglycemia (^{171})</td>
<td>1 (4/89)</td>
<td>4.5%</td>
</tr>
<tr>
<td></td>
<td>Anorexia(^{155})</td>
<td>1 (1/35)</td>
<td>3%</td>
</tr>
<tr>
<td></td>
<td>Diarrhea (^{153,189})</td>
<td>2 (6/114)</td>
<td>3%-12%</td>
</tr>
<tr>
<td></td>
<td>Asymptomatic hypotension(^{153})</td>
<td>1 (1/60)</td>
<td>2%</td>
</tr>
<tr>
<td></td>
<td>Nausea(^{171})</td>
<td>1 (2/89)</td>
<td>2%</td>
</tr>
<tr>
<td></td>
<td>Cold extremities(^{171})</td>
<td>1 (1/89)</td>
<td>1%</td>
</tr>
<tr>
<td></td>
<td>Restless sleep(^{171})</td>
<td>1 (1/89)</td>
<td>1%</td>
</tr>
<tr>
<td>Oral Propranolol 2-2.1 mg/kg/day</td>
<td>**Hypotension(^{18,167})</td>
<td>11 (89/944)</td>
<td>0.4%-62%</td>
</tr>
<tr>
<td></td>
<td>ECG changes(^{167})</td>
<td>1 (7/25)</td>
<td>28%</td>
</tr>
<tr>
<td></td>
<td>Bradycardia(^{151,167,173,190,191,199})</td>
<td>7 (51/577)</td>
<td>0.8%-38%</td>
</tr>
<tr>
<td></td>
<td>Nausea/Vomiting/Diarrhea(^{151,153,162,175,178,179,181,190-193})</td>
<td>12 (37/1048)</td>
<td>0.4%-24%</td>
</tr>
<tr>
<td></td>
<td>Cold extremities(^{151,163,178,180,193,200,202})</td>
<td>7 (17/626)</td>
<td>1%-10%</td>
</tr>
<tr>
<td></td>
<td>Sleep disturbance/Light sleep(^{153,162,175,178,179,190-193,203})</td>
<td>10 (88/729)</td>
<td>3%-29%</td>
</tr>
<tr>
<td></td>
<td>Behavioral changes(^{162,167,175,178,193,200})</td>
<td>6 (13/531)</td>
<td>0.5%-10.8%</td>
</tr>
<tr>
<td></td>
<td>Respiratory symptoms/Asthma/Dyspnea(^{151,162,163,165,176,180,190,192,194})</td>
<td>10 (35/725)</td>
<td>2%-10%</td>
</tr>
<tr>
<td></td>
<td>Fatigue/Somnolence(^{165,167,173,176,180,201})</td>
<td>6 (15/289)</td>
<td>1%-25.9%</td>
</tr>
<tr>
<td></td>
<td>Fever(^{162})</td>
<td>1 (2/30)</td>
<td>7%</td>
</tr>
<tr>
<td></td>
<td>Gross motor abnormalities(^{175})</td>
<td>1 (13/188)</td>
<td>7%</td>
</tr>
<tr>
<td></td>
<td>****Hypoglycemia(^{168,173,191,194,202})</td>
<td>5 (14/328)</td>
<td>2%-6.8%</td>
</tr>
<tr>
<td></td>
<td>Cutaneous symptoms/Rash(^{153,176,180})</td>
<td>3 (5/172)</td>
<td>2%-5%</td>
</tr>
<tr>
<td></td>
<td>Gastroesophageal issues(^{180,194})</td>
<td>2 (3/99)</td>
<td>2.3%-4%</td>
</tr>
<tr>
<td></td>
<td>Sweating(^{18,178})</td>
<td>2 (2/85)</td>
<td>2%-4%</td>
</tr>
<tr>
<td></td>
<td>Constipation(^{151,202})</td>
<td>2 (3/186)</td>
<td>0.8%-3%</td>
</tr>
<tr>
<td></td>
<td>Respiratory tract infection(^{162})</td>
<td>1 (1/30)</td>
<td>3%</td>
</tr>
<tr>
<td></td>
<td>Skin atrophy(^{156})</td>
<td>1 (2/50)</td>
<td>3%</td>
</tr>
<tr>
<td></td>
<td>Seizure(^{170})</td>
<td>1 (1/45)</td>
<td>2%</td>
</tr>
<tr>
<td></td>
<td>Agranulocytosis(^{163})</td>
<td>1 (1/97)</td>
<td>1%</td>
</tr>
<tr>
<td></td>
<td>Cyanotic breath-holding spells(^{183,184})</td>
<td>1 (1/71)</td>
<td>1%</td>
</tr>
<tr>
<td></td>
<td>Low body temperature(^{163})</td>
<td>1 (1/97)</td>
<td>1%</td>
</tr>
<tr>
<td></td>
<td>Stridor(^{183,184})</td>
<td>1 (1/71)</td>
<td>1%</td>
</tr>
<tr>
<td></td>
<td>Bronchospasm(^{168,193,203})</td>
<td>3 (3/337)</td>
<td>0.4%-2.7%</td>
</tr>
<tr>
<td></td>
<td>Worsening of ulceration(^{190})</td>
<td>1 (4/250)</td>
<td>1.6%</td>
</tr>
<tr>
<td></td>
<td>Peripheral cyanosis(^{190})</td>
<td>1 (2/250)</td>
<td>0.8%</td>
</tr>
<tr>
<td>Oral Propranolol 3-3.3 mg/kg/day</td>
<td>(^{1} )Sleep disturbances/Nightmares(^{156,164,166})</td>
<td>3 (14/99)</td>
<td>3%-23%</td>
</tr>
<tr>
<td></td>
<td>Transient asymptomatic hypotension(^{158,164})</td>
<td>2 (7/66)</td>
<td>3%-17%</td>
</tr>
<tr>
<td></td>
<td>Daytime drowsiness(^{164})</td>
<td>1 (6/35)</td>
<td>17%</td>
</tr>
<tr>
<td></td>
<td>Benign infections(^{164})</td>
<td>1 (4/35)</td>
<td>11%</td>
</tr>
<tr>
<td></td>
<td>Digestive symptoms(^{164})</td>
<td>1 (3/35)</td>
<td>9%</td>
</tr>
<tr>
<td></td>
<td>Constipation(^{152})</td>
<td>1 (2/30)</td>
<td>7%</td>
</tr>
<tr>
<td></td>
<td>Tachypnea(^{152})</td>
<td>1 (2/30)</td>
<td>7%</td>
</tr>
<tr>
<td></td>
<td>Irritability(^{164})</td>
<td>1 (2/35)</td>
<td>6%</td>
</tr>
<tr>
<td></td>
<td>Cold extremities(^{152,166})</td>
<td>2 (2/66)</td>
<td>3%</td>
</tr>
<tr>
<td></td>
<td>Esophageal reflux(^{158,166})</td>
<td>2 (2/64)</td>
<td>3%</td>
</tr>
<tr>
<td></td>
<td>Poor weight gain(^{164})</td>
<td>1 (1/35)</td>
<td>3%</td>
</tr>
<tr>
<td></td>
<td>Decreased appetite(^{164})</td>
<td>1 (1/35)</td>
<td>3%</td>
</tr>
<tr>
<td></td>
<td>Bradycardia(^{164})</td>
<td>1 (1/35)</td>
<td>3%</td>
</tr>
<tr>
<td></td>
<td>Hypoglycemia(^{152})</td>
<td>1 (1/30)</td>
<td>3%</td>
</tr>
<tr>
<td></td>
<td>Increased appetite(^{164})</td>
<td>1 (1/35)</td>
<td>3%</td>
</tr>
<tr>
<td></td>
<td>Shortness of breath on activity(^{164})</td>
<td>1 (1/35)</td>
<td>3%</td>
</tr>
<tr>
<td>Intervention</td>
<td>Harm/Adverse Event</td>
<td>Number of Studies (# Participants With Harm/Total Participants)</td>
<td>Reported Rates Across Studies</td>
</tr>
<tr>
<td>------------------------------------</td>
<td>-----------------------------------------</td>
<td>-----------------------------------------------------------------</td>
<td>-------------------------------</td>
</tr>
<tr>
<td><strong>Oral Propranolol 2-3 mg/kg/day</strong></td>
<td>Cold extremities\textsuperscript{16,172}</td>
<td>2 (64/206)</td>
<td>3%-36%</td>
</tr>
<tr>
<td></td>
<td>Nocturnal restlessness\textsuperscript{172}</td>
<td>1 (39/174)</td>
<td>22%</td>
</tr>
<tr>
<td></td>
<td>Daytime sleepiness/Inactivity\textsuperscript{172}</td>
<td>1 (28/174)</td>
<td>16%</td>
</tr>
<tr>
<td></td>
<td>Gastrointestinal symptoms\textsuperscript{172}</td>
<td>1 (12/174)</td>
<td>7%</td>
</tr>
<tr>
<td></td>
<td>Agitation\textsuperscript{16}</td>
<td>1 (2/32)</td>
<td>6%</td>
</tr>
<tr>
<td></td>
<td>Insomnia\textsuperscript{16}</td>
<td>1 (2/32)</td>
<td>6%</td>
</tr>
<tr>
<td></td>
<td>Restlessness/Increased daytime activity\textsuperscript{172}</td>
<td>1 (9/174)</td>
<td>5%</td>
</tr>
<tr>
<td></td>
<td>Hypotension\textsuperscript{16,172}</td>
<td>2 (7/206)</td>
<td>3%</td>
</tr>
<tr>
<td></td>
<td>Asthma/Wheezing\textsuperscript{16,172}</td>
<td>2 (18/206)</td>
<td>3%</td>
</tr>
<tr>
<td></td>
<td>Nightmares\textsuperscript{16}</td>
<td>1 (1/32)</td>
<td>3%</td>
</tr>
<tr>
<td></td>
<td>Sweating\textsuperscript{16}</td>
<td>1 (1/32)</td>
<td>3%</td>
</tr>
<tr>
<td></td>
<td>Feeding difficulties\textsuperscript{172}</td>
<td>1 (3/174)</td>
<td>2%</td>
</tr>
<tr>
<td></td>
<td>Ulceration (onset/worsening)\textsuperscript{172}</td>
<td>1 (4/174)</td>
<td>2%</td>
</tr>
<tr>
<td></td>
<td>Breath holding spells\textsuperscript{172}</td>
<td>1 (2/174)</td>
<td>1%</td>
</tr>
<tr>
<td><strong>††Oral Propranolol 1-4 mg/kg/day</strong></td>
<td>Somnolence\textsuperscript{185,195}</td>
<td>2 (5/83)</td>
<td>6%-6.7%</td>
</tr>
<tr>
<td></td>
<td>Hypoglycemia\textsuperscript{185}</td>
<td>1 (1/53)</td>
<td>2%</td>
</tr>
<tr>
<td></td>
<td>Hypotension\textsuperscript{185}</td>
<td>1 (1/53)</td>
<td>2%</td>
</tr>
<tr>
<td></td>
<td>Profound motting of extremities\textsuperscript{185}</td>
<td>1 (1/53)</td>
<td>2%</td>
</tr>
<tr>
<td></td>
<td>Severe bradycardia\textsuperscript{185}</td>
<td>1 (1/53)</td>
<td>2%</td>
</tr>
<tr>
<td></td>
<td>Cold extremities\textsuperscript{195}</td>
<td>1 (3/30)</td>
<td>10%</td>
</tr>
<tr>
<td></td>
<td>Bronchospasm\textsuperscript{195}</td>
<td>1 (3/30)</td>
<td>10%</td>
</tr>
<tr>
<td></td>
<td>Transaminase increase\textsuperscript{195}</td>
<td>1 (1/30)</td>
<td>3.3%</td>
</tr>
<tr>
<td><strong>Topical Propranolol 0.5-3%</strong></td>
<td>Skin changes (redness, rash, itching, erosion, eczema)\textsuperscript{197,198,204}</td>
<td>2 (9/249)</td>
<td>1.96%-4%</td>
</tr>
<tr>
<td></td>
<td>Ulceration\textsuperscript{204}</td>
<td>1 (5/148)</td>
<td>3%</td>
</tr>
</tbody>
</table>
Table 24. Adverse effects in case series of propranolol to treat IH (continued)

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Harm/Adverse Event</th>
<th>Number of Studies (# Participants With Harm/Total Participants)</th>
<th>Reported Rates Across Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral Propranolol + Atenolol (dose not clearly reported)</td>
<td>Cold extremities</td>
<td>1 (55/109)</td>
<td>51%</td>
</tr>
<tr>
<td></td>
<td>Sleep disturbance</td>
<td>1 (47/109)</td>
<td>43%</td>
</tr>
<tr>
<td></td>
<td>Gastrointestinal problems</td>
<td>1 (27/109)</td>
<td>25%</td>
</tr>
<tr>
<td></td>
<td>Fatigue</td>
<td>1 (20/109)</td>
<td>18%</td>
</tr>
<tr>
<td></td>
<td>Coughing</td>
<td>1 (19/109)</td>
<td>17%</td>
</tr>
<tr>
<td></td>
<td>Sweating</td>
<td>1 (16/109)</td>
<td>15%</td>
</tr>
<tr>
<td></td>
<td>Pallor</td>
<td>1 (14/109)</td>
<td>13%</td>
</tr>
<tr>
<td></td>
<td>Agitation/irritation</td>
<td>1 (14/109)</td>
<td>13%</td>
</tr>
<tr>
<td></td>
<td>Dyspnea/shortness of breath</td>
<td>1 (6/109)</td>
<td>6%</td>
</tr>
<tr>
<td></td>
<td>Increased activity</td>
<td>1 (5/109)</td>
<td>5%</td>
</tr>
<tr>
<td></td>
<td>Skin reaction</td>
<td>1 (5/109)</td>
<td>5%</td>
</tr>
<tr>
<td></td>
<td>Nausea/vomiting</td>
<td>1 (4/109)</td>
<td>4%</td>
</tr>
<tr>
<td></td>
<td>Decreased appetite</td>
<td>1 (4/109)</td>
<td>4%</td>
</tr>
<tr>
<td></td>
<td>Increased appetite</td>
<td>1 (3/109)</td>
<td>3%</td>
</tr>
<tr>
<td></td>
<td>Hypoglycemia</td>
<td>1 (3/109)</td>
<td>3%</td>
</tr>
<tr>
<td></td>
<td>Syncope</td>
<td>1 (2/109)</td>
<td>2%</td>
</tr>
<tr>
<td></td>
<td>Dizziness</td>
<td>1 (2/109)</td>
<td>2%</td>
</tr>
<tr>
<td></td>
<td>Hair loss</td>
<td>1 (2/109)</td>
<td>2%</td>
</tr>
<tr>
<td></td>
<td>Seizure</td>
<td>1 (1/109)</td>
<td>1%</td>
</tr>
<tr>
<td></td>
<td>Dry mouth (xerostomia)</td>
<td>1 (1/109)</td>
<td>1%</td>
</tr>
<tr>
<td></td>
<td>Hallucinations</td>
<td>1 (1/109)</td>
<td>1%</td>
</tr>
</tbody>
</table>

ALT = alanine aminotransferase; AST = aspartate transaminase; IH = infantile hemangioma; kg = kilogram; mg = milligram
*One study of 1.5 mg/kg/day (not included in table) reported that 23 of 109 children had adverse events (N of events not stated) including hypotension, insomnia, agitation, aggravation of bronchitis, cold extremities gastroesophageal issues, and dry skin. Four children discontinued propranolol due to aggravation of bronchitis (n=2) or gastroesophageal issues (n=2).
**One study 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). Some children in another study were also receiving steroids (n=20/76) or timolol (n=7/76) along with propranolol. In a third study evaluating propranolol, 29 of 250 children were also receiving concurrent steroids.
***One study reported “lethargy, viral illness, and hypoglycemia” in 2/250 children (data not factored into table).
†One study reported discontinuation of propranolol in 4/35 children because of “insomnia, nightmares, loss of energy.” These data are not factored into the table.
††Adverse events in Blatt 2011 were considered serious by the study investigators.
†††Raphael 2015 is related to de Graaf 2013 but the extent of overlap is unclear. The case series also reports harms in 3 individual case reports: among 45 children receiving 4 mg/kg/day propranolol, 1 had multiple episodes of decreased consciousness, 1 had nausea, 1 had an epileptic seizure after the first propranolol dose. Among those 64 receiving 3 mg/kg/day of atenolol, 1 had difficulty waking and hypotonia, 1 had two episodes of loss of consciousness, 1 had three episodes of loss of consciousness.

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 Hemangeol® in pediatric patients has been reported in the medication package insert. 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. 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. 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.

**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. 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 comparative studies addressing this Key Question.

**Key Question 4. Effectiveness and Harms of Surgical Interventions**

**Key Points**

- Studies primarily addressed different laser modalities compared with observation or other laser modalities. 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 for difference in effects on size reduction between longer pulse PDL and other lasers).
- Two small studies addressed different surgical techniques (cryotherapy, intense pulsed light photothermolysis, sclerosis) and reported some positive effects in reducing IH size or improving appearance, but their smaller size and low quality preclude conclusions (insufficient SOE).
- 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 CO₂ 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 and pigmentation changes).

Overview of the Literature

Eleven comparative studies (three RCTs,210-212 seven retrospective cohort studies,213-219 and one prospective comparative study that used treated and untreated lesions and intervention and control groups220) and 30 case series addressed surgical approaches. The RCTs were conducted in the Netherlands,210 Japan,211 and the UK.212 Cohort studies were performed in the United States,216,217 Greece,218 Singapore,213 Russia,219 and Germany.214,215 Two RCTs210,212 compared PDL to observation; one used traditional PDL in infants aged 1 to 14 weeks,212 and the second used PDL with epidermal cooling in infants aged 0 to 6 months.210 The third RCT211 compared the use of non-cooled traditional PDL to longer pulse PDL with epidermal cooling in infants between 1 and 3 months old. We considered RCTs to be of good210 and fair quality.211,212

Cohort studies examined various comparisons between different laser types including PDL versus Nd:YAG,215 Argon versus Nd:YAG,217 short pulse PDL versus longer pulse PDL.213 One compared Nd:YAG and CO₂ lasers and also included a non-surgical comparison group for airway IH.214 Two studies compared different skin cooling protocols with the same laser types, including Nd:YAG218 and PDL.216 One cohort study compared cryosurgery, photothermolysis with intense pulsed light, and photothermolysis plus sclerosis with alcohol and lidocaine.219 We considered two cohort studies as fair quality,213,218 and the rest as poor.214-217,219 We considered the self-controlled comparative study (rated using the Newcastle Ottawa tool) as poor quality.220

Overall, longer pulse PDL with epidermal cooling was the most commonly used laser for cutaneous lesions and Nd:YAG was the most commonly used intralesionally. Most studies reported a higher success rate with longer pulse PDL compared to observation in managing the size of IH, although the magnitude of effect differed substantially. CO₂ laser was used for subglottic IH in a single study, and was noted to have a higher success rate and lower complication rate than both Nd:YAG and observation. Studies addressing other surgical approaches (cryosurgery, intense pulsed light thermolysis) reported some improvements in IH but included few participants in each arm (total n = 263).

SOE for outcomes after laser and surgical 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 CO₂ lasers, all studies were limited by sample size, and SOE was insufficient for all outcome parameters.

Thirty case series reported on harms of surgical approaches for IH (3831 children). Seventeen case series reported on harms from laser treatments, including 10 studies of PDL,221-
four studies of Nd:YAG lasers,231-234 one of combined PDL and Nd:YAG,235 one of long-pulse Alexandrite laser,236 and one report of carbon dioxide laser.237 Most studies included children with IH in multiple locations; one included children with only airway IH.237 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,223 two of fair quality,227,230 and 14 of poor quality.221,222,224-226,228,229,231-237 We rated one cohort study that compared propranolol with concurrent PDL or followed by PDL and two comparing laser and topical timolol as poor quality for harms reporting and discuss harms of PDL here and harms of propranolol in the beta-blocker section of KQ2 above.14,106,150

Thirteen case series (840 children) reported harms from surgical procedures, typically excision or resection, to treat IH.238-249 Ages ranged from 1 month to 19 years. The majority of studies focused on treatment of facial IH, including three studies of lip IH,240,244,248 two series of periocular/periorbital IH,242,245 two reports of various facial locations,241,247 and one study of nasal tip IH.243 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 RCT210 randomized 22 children with IH between 0 and 6 months of age into equal groups of observation or PDL with epidermal cooling. Twelve-month size change scores were used for analysis. Further, parents were asked to answer 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 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 improvement in the IH at 12 months compared with 33 percent 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.212,250 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. 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 of 117 children (32 of 57 in the PDL arm had complete clearance vs. 27 of 60 in the observation arm, p=0.31 and 41 of 57 and 48 of 60 had minimal residual signs, p=0.39). Table 25 outlines key outcomes.
### Table 25. Key resolution outcomes in studies comparing PDL and observation

<table>
<thead>
<tr>
<th>Author, Year Groups (n)</th>
<th>Age, Months Type</th>
<th>Location</th>
<th>Methods and Measures of Resolution/Response</th>
<th>Resolution Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kessels et al. 2013210</td>
<td>Age, median (range)</td>
<td>G1+G2: multiple</td>
<td>• Photographs • Color measured by reflectance photometer • Improvement scale evaluated by blinded panel 1= no improvement 2= moderate improvement 3 = significant improvement</td>
<td>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</td>
</tr>
<tr>
<td>G1: Pulsed dye laser (11)</td>
<td>G1: 3 (1.7-5.0) G2: 3 (1.5-4.5)</td>
<td>Type Superficial and cutaneous only</td>
<td></td>
<td>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</td>
</tr>
<tr>
<td>G2: Observation (11)</td>
<td></td>
<td></td>
<td></td>
<td>Color change, median (interquartile range) G1: 10.16 (5.50 to 15.41) G2: 4.23 (0.84 to 9.28) G1 vs.G2 p= 0.03</td>
</tr>
<tr>
<td>Quality: Good</td>
<td></td>
<td></td>
<td></td>
<td>Complete clearance or minimum residual signs, n (%) G1: 25 (42) G2: 27 (44) G1 vs.G2: p=0.92</td>
</tr>
<tr>
<td>Batta et al. 2002212</td>
<td>Age, median (range, days)</td>
<td>G1+G2: multiple</td>
<td>• Photographs • Primary outcome measure assessed by investigator: complete clearance or minimum residual signs at age 1 year • Blinded medical observer assessed redness (secondary outcome measure)</td>
<td>Complete clearance or minimum residual signs, n (%) G1: 25 (42) G2: 27 (44) G1 vs.G2: p=0.92</td>
</tr>
<tr>
<td>G1: Pulsed dye laser (60)</td>
<td>G1: 38 (10 to 101) G2: 32 (5 to 79)</td>
<td>Type, n (%) Flat G1: 31 (52) G2: 30 (49) Raised G1: 29 (48) G2: 31 (51)</td>
<td></td>
<td>Complete only G1: 18 (30) G2: 3 (5) G1 vs.G2: p=0.001</td>
</tr>
<tr>
<td>G2: Observation (61)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quality: Fair</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*G = group; n = number; PDL = pulsed dye laser*

### Comparative Effectiveness of Various PDL Modalities

One fair quality Japanese RCT211 randomized 52 patients to a “traditional PDL” group and a “long-pulse” dye laser group (pulse durations of 0.45 milliseconds vs. 10-20 milliseconds). 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 longer pulse PDL group compared with the traditional PDL group (177 days, p=0.01). Another fair quality cohort study comparing short and longer 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.213 In a poor quality cohort study evaluating cryogen spray cooling as an adjunct to PDL versus no cooling in 164 children (mean age overall= 2 years, 11 months), c216 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).216 Changes in color did not differ between groups. Table 26 outlines key outcomes.
Table 26. Key resolution outcomes in studies comparing PDL modalities

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Groups (n)</th>
<th>Quality</th>
<th>Age, Months</th>
<th>Location</th>
<th>Methods and Measures of Resolution/Response</th>
<th>Resolution Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kono et al. 2005¹¹¹</td>
<td>G1: Long-pulse dye laser (26)</td>
<td>Fair</td>
<td>Type</td>
<td>G1+G2: multiple</td>
<td>• Serial photographs assessed by blinded medical observer using: Excellent: 76-100% Moderate: 51-75% Mild: 26-50% None or worse (0-25%)</td>
<td>Complete clearance or minimal residual signs at 1 year, n (%)</td>
</tr>
<tr>
<td></td>
<td>G2: Traditional pulsed dye laser (26)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>G1: 17 (65) G2: 14 (54) G1 vs. G2 p=0.397</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Age, mean±SD, weeks</td>
<td>G1: 11.2 G2: 10.7</td>
<td></td>
<td>Excellent G1: 17 G2: 14</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Type, %</td>
<td>Superficial G1+G2: 100</td>
<td></td>
<td>Moderate G1: 7 G2: 5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mild G1: 2 G2: 4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>None or worse G1: 0 G2: 3</td>
</tr>
<tr>
<td>Tay et al. 2012¹³</td>
<td>G1: Short pulse 595-nm Pulsed dye laser (15)</td>
<td>Fair</td>
<td>Age mean (range)</td>
<td>G1+G2: 6.5 (2.5-19)</td>
<td>• Photographs evaluated by unblinded dermatologist</td>
<td>Number of treatments needed for resolution</td>
</tr>
<tr>
<td></td>
<td>G2: Longer pulse 595-nm PDL (8)</td>
<td></td>
<td>Type, n</td>
<td>Superficial G1: 7 G2: 3</td>
<td></td>
<td>G1: 3-14 mean=8 median=7 G2: 4-14 mean=9 median=7 G1 vs. G2: p=ns</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mixed G1: 8 G2: 5</td>
<td></td>
<td>Average number of treatments needed for the clearance of mixed IH= 4 to 5 treatments more in both groups</td>
</tr>
</tbody>
</table>
Table 26. Key resolution outcomes in studies comparing PDL modalities (continued)

<table>
<thead>
<tr>
<th>Author, Year Groups (n) Quality</th>
<th>Age, Months Type</th>
<th>Location</th>
<th>Methods and Measures of Resolution/Response</th>
<th>Resolution Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chang et al. 2001&lt;sup&gt;216&lt;/sup&gt; G1: Non cooled flash lamp-pumped pulsed dye laser (82) G2: Cryogen spray cooling plus flash lamp-pumped pulse dyed laser (82)</td>
<td>Age, mean, years G1: 2.5 G2: 3.4</td>
<td>G1+G2: multiple</td>
<td>• Photographs assessed by blinded plastic surgeons • Volume reduction, texture, color • Excellent: 76-100% improvement Good: 51-75% Fair: 26-50% Poor:0-25%</td>
<td>Volume reduction, mean score G1: 3.84 G2: 3.96 G1 vs.G2 p=0.008</td>
</tr>
<tr>
<td></td>
<td>Type, % Cutaneous G1+G2: 100</td>
<td></td>
<td></td>
<td>Texture G1: 3.57 G2: 3.90 G1 vs.G2 p=0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Color G1: 3.98 G2: 4.00 G1 vs.G2 p=0.155</td>
</tr>
</tbody>
</table>

G = group; n = number; nm = nanometer; 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<sup>217</sup>, traditional PDL<sup>215</sup>, or CO<sub>2</sub> laser or observation<sup>214</sup>. 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%).<sup>217</sup> 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).<sup>215</sup> 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.<sup>214</sup> 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<sub>2</sub> laser. All patients with severe airway obstruction from the hemangioma were treated with tracheostomy. 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<sub>2</sub> 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<sub>2</sub> 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<sub>2</sub> 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 27 outlines key outcomes.

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

<table>
<thead>
<tr>
<th>Author, Year Groups (n) Quality</th>
<th>Age, Months Type</th>
<th>Location</th>
<th>Methods and Measures of Resolution/Response</th>
<th>Resolution Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nicolai et al. 2005&lt;sup&gt;214&lt;/sup&gt; G1: No laser (14) G2: Nd:YAG laser (14) G3: CO2 laser (17) Quality: Poor</td>
<td>Age NR</td>
<td>G1+G2+G3: airway</td>
<td>• Resolution not assessed</td>
<td>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</td>
</tr>
</tbody>
</table>

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). 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 28).

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Groups (n)</th>
<th>Quality</th>
<th>Age, Months Type</th>
<th>Location</th>
<th>Methods and Measures of Resolution/Response</th>
<th>Resolution Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vlachakis et al. 2004</td>
<td>G1: Nd:YAG laser, cooled with ice before, during and after irradiation (120) G2: Nd:YAG laser, cooled with ice only during irradiation (115)</td>
<td>Fair</td>
<td>Age mean (range) G1+G2: 9 (3 months to 4 years) Type, % Cutaneous G1+G2: 100</td>
<td>G1+G2: multiple</td>
<td>• Change in size Excellent: 90-100% area reduction Good: 50-89% Moderate: 20-49% Poor: 0-19% • Blinded assessment: NR</td>
<td>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</td>
</tr>
</tbody>
</table>

| Abbreviations: G = group; n = number; Nd:YAG = neodymium yttrium aluminium garnet; NR = not reported |

Effectiveness of Surgical Treatments

Photothermolysis With Intense Pulsed Light Compared With Cryosurgery Compared With Photothermolysis With Intense Pulsed Light Plus Sclerosis

One retrospective cohort study compared three treatment modalities in 250 infants <12 months old) with maxillofacial IH: cryosurgery, photothermolysis with intense pulsed light, and photothermolysis plus sclerosis with alcohol and lidocaine (Table 29). More children in the combined group had a size reduction of at least 50 percent after one treatment session than in the cryosurgery or laser arms (60 vs. 18 vs. 31, respectively, p=NR). Four children in the combined arm, 17 in the laser arm, and 24 in the cryosurgery arm had less than 10 percent decrease in IH size. Time to IH regression was reduced by 4.2 months for the combined arm compared with the laser arm and was 10.7 months shorter compared with the cryosurgery arm (p=NR). Children in combined arm required an average of 2.6 treatment sessions compared with 4.5 in the laser arm and 3.7 in the cryosurgery arm (p=NR).
Table 29. Key resolution outcomes in comparative studies of photothermolysis with intense pulsed light and cryosurgery

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Groups (n)</th>
<th>Quality</th>
<th>Age, Months Type</th>
<th>Location</th>
<th>Methods and Measures of Resolution/Response</th>
<th>Resolution Outcomes</th>
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<tbody>
<tr>
<td>Ryzhevskiy et al.</td>
<td>G1: Selective photothermolysis (87) G2: Cryo-destruction with liquid nitrogen (79) G3: Combination of selective photothermolysis and sclerosis (84)</td>
<td>Poor</td>
<td>G1+G2: 9 (3 months to 4 years)</td>
<td>G1+G2: multiple</td>
<td>- Lesion area measured with graph paper. Change in depth confirmed by ultrasound - Cosmetic results after first treatment session: Good: 50% or more reduction in area; Satisfactory: 10-50% reduction; Unsatisfactory: &lt; 10% or no positive dynamics - Evaluation blinding: NR</td>
<td>Resolution after session 1, %</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Good</td>
<td>G1: 35.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>G2: 22.8</td>
<td>G3: 71.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Satisfactory</td>
<td>G1: 44.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>G2: 46.8</td>
<td>G3: 23.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Unsatisfactory</td>
<td>G1: 19.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>G2: 30.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>G3: 4.8</td>
</tr>
</tbody>
</table>

G = group; NR = not reported

Cryosurgery Versus No Treatment

One study assessed cryosurgical treatment of IH in preterm infants with multiple IH by treating one IH lesion and not treating another.220 Some children had more than one pair of treated/untreated lesions, and the study followed infants up to age 1 or 2 years. Thirteen of 17 treated IH and two of 17 untreated IH met the primary endpoint of intact, IH-free skin with mild or no pigmentation or scarring at 1 or 2 years of age (p<0.001). Fifteen of 17 IH in the control arm had residual signs at the final followup and one had scarring, compared with four IH with scarring in the cryosurgery arm (p<0.001). Table 30 outlines outcomes.
Table 30. Key resolution outcomes in comparative studies of cryosurgical therapy

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Groups (n)</th>
<th>Quality</th>
<th>Age, Months</th>
<th>Location</th>
<th>Methods and Measures of Resolution/Response</th>
<th>Resolution Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>G2: no treatment control (13)</td>
<td></td>
<td>(preterm infants)</td>
<td></td>
<td></td>
<td>G1: 13/17 IH (76)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>G2: 2/17 (12)</td>
<td>G1 vs G2: p&lt;0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Residual signs, n IH (%)</td>
<td>G1: 4 (24)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>G2: 15 (88)</td>
<td>G1 vs G2: p&lt;0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Scarring, n IH (%)</td>
<td>G1: 4 (24)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>G2: 0</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Residual IH, n (%)</td>
<td>G1: 0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>G2: 14 (82)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Relapse, n</td>
<td>G1+G2: 0</td>
</tr>
</tbody>
</table>

IH = infantile hemangioma; n = number; NR = not reported

Harms of Laser and 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 with 5-year followup of children treated early with PDL, the number of children in the PDL arm with skin atrophy did not differ significantly from that in the observation arm (13 of 57 vs. 7 of 60, p=0.14), but more children in the PDL arm had hypopigmentation (25 vs. 14, p=0.03). Numbers requiring surgical correction did not differ significantly between groups (4 in PDL arm vs. 2 in observation). In one RCT comparing traditional PDL and longer pulse PDL, hyperpigmentation, hypopigmentation, and negative textural changes were all significantly greater in the traditional PDL group (p values <0.01). In a cohort study comparing short and longer 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. One study comparing topical timolol and timolol plus PDL reported that no harms occurred in either group, while another comparing timolol and PDL plus Nd:YAG laser reported minor crusting and hyperpigmentation in four of 30 children. Studies typically included a limited number of participants and may not have been adequately powered to detect harms. Table 31 outlines harms reported in comparative studies.
Table 31. Harms/adverse effects in comparative studies of lasers to treat infantile hemangioma (IH)

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Harm/Adverse Event</th>
<th>N Studies Reporting Harm (# Participants With Harm/Total Participants)</th>
<th>Reported Rates Across Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulsed dye laser</td>
<td>Purpura&lt;sup&gt;215&lt;/sup&gt;</td>
<td>1 (25/25)</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td>Swelling&lt;sup&gt;215&lt;/sup&gt;</td>
<td>1 (25/25)</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td>Skin atrophy&lt;sup&gt;212&lt;/sup&gt;</td>
<td>1 (17/60)</td>
<td>28%</td>
</tr>
<tr>
<td></td>
<td>Minimal crusting&lt;sup&gt;210&lt;/sup&gt;</td>
<td>1 (2/11)</td>
<td>18.2%</td>
</tr>
<tr>
<td></td>
<td>Ulceration&lt;sup&gt;212&lt;/sup&gt;</td>
<td>1 (4/60)</td>
<td>7%</td>
</tr>
<tr>
<td></td>
<td>Painful ulceration&lt;sup&gt;212&lt;/sup&gt;</td>
<td>1 (3/60)</td>
<td>5%</td>
</tr>
<tr>
<td></td>
<td>Ulcer formation&lt;sup&gt;211&lt;/sup&gt;</td>
<td>1 (1/26)</td>
<td>4%</td>
</tr>
<tr>
<td></td>
<td>Bleeding&lt;sup&gt;212&lt;/sup&gt;</td>
<td>1 (2/60)</td>
<td>3%</td>
</tr>
<tr>
<td></td>
<td>Infection&lt;sup&gt;212&lt;/sup&gt;</td>
<td>1 (2/60)</td>
<td>3%</td>
</tr>
<tr>
<td></td>
<td><strong>Atrophic scarring</strong></td>
<td>1 (2/42)</td>
<td>3%-6%</td>
</tr>
<tr>
<td></td>
<td>Hyperpigmentation&lt;sup&gt;211,213,215&lt;/sup&gt;</td>
<td>3 (12/66)</td>
<td>13%-20%</td>
</tr>
<tr>
<td></td>
<td>Texture change&lt;sup&gt;211,213&lt;/sup&gt;</td>
<td>2 (8/41)</td>
<td>13%-23%</td>
</tr>
<tr>
<td></td>
<td>Hypopigmentation&lt;sup&gt;211,213,215&lt;/sup&gt;</td>
<td>4 (41/126)</td>
<td>10%-45%</td>
</tr>
<tr>
<td></td>
<td>Blistering (crusts and blisters)&lt;sup&gt;213,215&lt;/sup&gt;</td>
<td>2 (21/40)</td>
<td>13%-76%</td>
</tr>
<tr>
<td>Longer pulse PDL</td>
<td>Hypopigmentation&lt;sup&gt;211,213&lt;/sup&gt;</td>
<td>2 (4/34)</td>
<td>12%-12.5%</td>
</tr>
<tr>
<td></td>
<td>Hyperpigmentation&lt;sup&gt;211,213&lt;/sup&gt;</td>
<td>2 (3/34)</td>
<td>8%-12.5%</td>
</tr>
<tr>
<td></td>
<td>Texture change&lt;sup&gt;211,213&lt;/sup&gt;</td>
<td>2 (2/34)</td>
<td>4%-12.5%</td>
</tr>
<tr>
<td>Nd:YAG laser&lt;sup&gt;215&lt;/sup&gt;</td>
<td>Hypopigmentation&lt;sup&gt;215&lt;/sup&gt;</td>
<td>1 (2/25)</td>
<td>6%</td>
</tr>
<tr>
<td></td>
<td>Purpura&lt;sup&gt;215&lt;/sup&gt;</td>
<td>1 (5/25)</td>
<td>20%</td>
</tr>
<tr>
<td></td>
<td>Crusts and blisters&lt;sup&gt;215&lt;/sup&gt;</td>
<td>1 (8/25)</td>
<td>24%</td>
</tr>
<tr>
<td></td>
<td>Swelling&lt;sup&gt;215&lt;/sup&gt;</td>
<td>1 (25/25)</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td>Atrophic scarring&lt;sup&gt;215&lt;/sup&gt;</td>
<td>1 (1/25)</td>
<td>3%</td>
</tr>
<tr>
<td></td>
<td>Scarring&lt;sup&gt;217&lt;/sup&gt;</td>
<td>1 (8/26)</td>
<td>30.8%</td>
</tr>
<tr>
<td></td>
<td>Delayed healing&lt;sup&gt;217&lt;/sup&gt;</td>
<td>1 (1/26)</td>
<td>12.5%</td>
</tr>
<tr>
<td></td>
<td>Postoperative bleeding&lt;sup&gt;217&lt;/sup&gt;</td>
<td>1 (2/26)</td>
<td>7.7%</td>
</tr>
<tr>
<td></td>
<td>Postoperative complications</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(including bleeding, atrophic scars</td>
<td>1 (35/235)</td>
<td>14.9%</td>
</tr>
<tr>
<td></td>
<td>and hypertrophic scars)&lt;sup&gt;218&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Argon laser</td>
<td>Delayed healing&lt;sup&gt;217&lt;/sup&gt;</td>
<td>1 (2/31)</td>
<td>13%</td>
</tr>
<tr>
<td></td>
<td>Postoperative bleeding&lt;sup&gt;217&lt;/sup&gt;</td>
<td>1 (1/31)</td>
<td>3.2%</td>
</tr>
<tr>
<td></td>
<td>Reaction to local anesthesia</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(seizure and hospitalization)&lt;sup&gt;217&lt;/sup&gt;</td>
<td>1 (1/31)</td>
<td>3.2%</td>
</tr>
<tr>
<td>Observation</td>
<td>Hypopigmentation&lt;sup&gt;212&lt;/sup&gt;</td>
<td>1 (9/61)</td>
<td>15%</td>
</tr>
<tr>
<td></td>
<td>Skin atrophy&lt;sup&gt;212&lt;/sup&gt;</td>
<td>1 (5/61)</td>
<td>8%</td>
</tr>
<tr>
<td></td>
<td>Ulceration&lt;sup&gt;212&lt;/sup&gt;</td>
<td>1 (4/61)</td>
<td>7%</td>
</tr>
<tr>
<td></td>
<td>Painful ulceration&lt;sup&gt;212&lt;/sup&gt;</td>
<td>1 (2/61)</td>
<td>3%</td>
</tr>
<tr>
<td></td>
<td>Bleeding&lt;sup&gt;212&lt;/sup&gt;</td>
<td>1 (2/61)</td>
<td>3%</td>
</tr>
<tr>
<td></td>
<td>Infection&lt;sup&gt;212&lt;/sup&gt;</td>
<td>1 (4/61)</td>
<td>7%</td>
</tr>
</tbody>
</table>

IH = infantile hemangioma; n = number; Nd:YAG = neodymium yttrium aluminum garnet; PDL = pulsed dye laser

*One study of cryosurgery reported harms by number of IH. Scarring occurred in 4/17 treated IH and on 1 untreated IH.220

**One study reported atrophic scarring and ulceration in 1/17 children receiving PDL and concurrent propranolol.150 One study (not represented in table) reported that 12.4% of the parents of 11 children receiving PDL judged that the treatment was painful. Another study included followup at 5 years post-PDL or observation and noted more scarring in the PDL group (49% vs 28% in controls, p=0.02 and more hypopigmentation (44% vs 23% in observation group, p=0.03). The number with skin atrophy was similar between groups.212,250

***One cohort study comparing topical timolol with PDL plus Nd:YAG laser reported crusting and hyperpigmentation in 4/30 children.14 Another study comparing topical timolol plus PDL to timolol alone reported that no children experienced any adverse effects.106

Ten case series reported on 1785 children who were treated with PDL (Table 32). 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.223 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. 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. Another fair quality case series of hand hemangiomas noted atrophy, pigment change, ulceration and scarring. The most frequently reported harms were hyperpigmentation (1% to 14% in four studies) and hypopigmentation (0-25% in five studies). Ulceration was also noted in three studies. Two studies reported no adverse events, and another reported no permanent side effects but cases of hyper and hypopigmentation.

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%). Another larger study with 160 participants reported complications including delayed healing, postoperative infection and scarring in 10 percent of their patients. A single case series of 31 patients with subglottic IH noted one case of respiratory distress related to the ventilation system.  

Table 32. Adverse effects in case series of laser treatments for IH

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Harm/Adverse Event</th>
<th>Number of Studies (# Participants With Harm/Total Participants)</th>
<th>Reported Rates Across Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulsed dye laser</td>
<td>Hyperpigmentation</td>
<td>221, 223, 225</td>
<td>4 (17/357)</td>
</tr>
<tr>
<td></td>
<td>Hypopigmentation</td>
<td>221, 223, 226, 228</td>
<td>5 (192/1014)</td>
</tr>
<tr>
<td></td>
<td>Pigment change (increase or decrease)</td>
<td>228, 230</td>
<td>2 (67/700)</td>
</tr>
<tr>
<td></td>
<td>Ulceration</td>
<td>224, 228, 230</td>
<td>3 (7/790)</td>
</tr>
<tr>
<td></td>
<td>Blisters</td>
<td>221</td>
<td>1 (3/62)</td>
</tr>
<tr>
<td></td>
<td>Atrophy</td>
<td>228, 230</td>
<td>2 (50/700)</td>
</tr>
<tr>
<td></td>
<td>Scarring</td>
<td>228, 230</td>
<td>2 (7/700)</td>
</tr>
<tr>
<td></td>
<td>Granuloma telangiectaticum</td>
<td>229</td>
<td>1 (4/548)</td>
</tr>
<tr>
<td></td>
<td>Cutaneous atrophy and pigmentation</td>
<td>230</td>
<td>1 (22/657)</td>
</tr>
<tr>
<td></td>
<td>Cutaneous atrophy and hypopigmentation</td>
<td>228</td>
<td>1 (32/657)</td>
</tr>
<tr>
<td>Nd:YAG laser</td>
<td>Scarring</td>
<td>222, 224</td>
<td>2 (36/794)</td>
</tr>
<tr>
<td></td>
<td>Hypertrophic scarring</td>
<td>234</td>
<td>1 (2/110)</td>
</tr>
<tr>
<td></td>
<td>Ulceration</td>
<td>232</td>
<td>1 (15/684)</td>
</tr>
<tr>
<td></td>
<td>Skin burn</td>
<td>232</td>
<td>1 (75/684)</td>
</tr>
<tr>
<td></td>
<td>Bleeding</td>
<td>32, 234</td>
<td>2 (13/794)</td>
</tr>
<tr>
<td></td>
<td>Nerve injury</td>
<td>232</td>
<td>1 (9/684)</td>
</tr>
<tr>
<td></td>
<td>Infection</td>
<td>32</td>
<td>1 (45/684)</td>
</tr>
<tr>
<td></td>
<td>Undesirable texture change</td>
<td>232</td>
<td>1 (30/684)</td>
</tr>
<tr>
<td></td>
<td>Anemia and hyperkalemia</td>
<td>232</td>
<td>1 (1/684)</td>
</tr>
<tr>
<td></td>
<td>Postoperative stenosis</td>
<td>233</td>
<td>1 (1/53)</td>
</tr>
<tr>
<td>CO₂ laser</td>
<td>Respiratory distress</td>
<td>237</td>
<td>1 (1/31)</td>
</tr>
<tr>
<td></td>
<td>Subglottic scarring</td>
<td>237</td>
<td>1 (1/31)</td>
</tr>
</tbody>
</table>
Table 32. Adverse effects in case series of laser treatments for IH (continued)

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Harm/Adverse Event</th>
<th>Number of Studies (# Participants With Harm/Total Participants)</th>
<th>Reported Rates Across Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Long-pulse Alexandrite laser</td>
<td>Hypopigmentation^{236}</td>
<td>1 (48)</td>
<td>2.1%</td>
</tr>
<tr>
<td></td>
<td>Blistering^{236}</td>
<td>1 99/48)</td>
<td>18.8%</td>
</tr>
<tr>
<td></td>
<td>Marked edema and erosion without residual scarring^{236}</td>
<td>1 (1/48)</td>
<td>2.1%</td>
</tr>
<tr>
<td>Combination (Pulsed Dye and ND:YAG)</td>
<td>Blistering^{235}</td>
<td>1 (17/37)</td>
<td>45.9%</td>
</tr>
<tr>
<td></td>
<td>Erosion^{235}</td>
<td>1 (1/37)</td>
<td>2.7%</td>
</tr>
<tr>
<td></td>
<td>Scarring^{235}</td>
<td>1 (1/37)</td>
<td>2.7%</td>
</tr>
</tbody>
</table>

CO₂ = carbon dioxide; IH = infantile hemangioma; Nd:YAG = neodymium yttrium aluminum garnet
One study^{227} noted “some” scarring. One study^{231} reported complications of “delayed healing, infection and/or scar formation” in 16/160 (10%) of participants. One study^{229} noted transient hypo- or hyperpigmentation in approximately 7% of cases and small atrophic scars in 4%.

Table 33 outlines harms reported in surgical case series and in one comparative study of cryosurgery.{superscript}220 Dehiscence rates ranged from 1.4 percent to 5.5 percent in five studies,^{238,240,246,248,251} and single cases of postoperative trauma-related wound dehiscence were reported in an additional three studies.{superscript}238,241,243 Postoperative infections were noted in two studies.{superscript}240,249 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.{superscript}247 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 3 years after treatment.{superscript}244 Harms reported in one study of cryosurgery included scarring in treated and untreated lesions.{superscript}220

Table 33. Adverse effects in case series of surgical treatments for IH

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Harm/Adverse Event</th>
<th>Number of Studies (# Participants With Harm/Total Participants)</th>
<th>Reported Rates Across Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery including excision and resection</td>
<td>Dehiscences^{238,240,246,248,251}</td>
<td>5 (17/357)</td>
<td>1.4%-5.5%</td>
</tr>
<tr>
<td></td>
<td>Postoperative traumatic wound dehiscence^{238,241,243}</td>
<td>3 (3/119)</td>
<td>2.3%-2.8%</td>
</tr>
<tr>
<td></td>
<td>Wound infections minor or dehiscence^{241}</td>
<td>1 (6/44)</td>
<td>13.6%</td>
</tr>
<tr>
<td></td>
<td>Postoperative infection^{240,249}</td>
<td>2 (1/264)</td>
<td>0-2%</td>
</tr>
<tr>
<td></td>
<td>Postoperative hematoma^{245}</td>
<td>1 (1/67)</td>
<td>1.5%</td>
</tr>
<tr>
<td></td>
<td>Intraoperative bleeding^{249}</td>
<td>1 (2/50)</td>
<td>4%</td>
</tr>
<tr>
<td></td>
<td>Skin necrosis^{243,245}</td>
<td>2 (3/106)</td>
<td>2.6%-3%</td>
</tr>
<tr>
<td></td>
<td>Hypertrophic scarring/cheloids^{248,251}</td>
<td>2 (10/142)</td>
<td>4%-9.8%</td>
</tr>
<tr>
<td></td>
<td>Incomplete excision with scarring^{249}</td>
<td>1 (1/50)</td>
<td>2%</td>
</tr>
<tr>
<td></td>
<td>Facial paresis, transient postop^{239}</td>
<td>1 (4/43)</td>
<td>9.3%</td>
</tr>
<tr>
<td></td>
<td>Permanent palsy of facial nerve^{239}</td>
<td>1 (1/43)</td>
<td>2.3%</td>
</tr>
<tr>
<td></td>
<td>Hemorrhage and ulceration^{244}</td>
<td>1 (3/127)</td>
<td>2.4%</td>
</tr>
<tr>
<td></td>
<td>Hypopigmentation of the skin or vermilion of the lip^{244}</td>
<td>1 (5/127)</td>
<td>3.9%</td>
</tr>
<tr>
<td></td>
<td>Labial mucoceles observed 3 years post- surgery^{244}</td>
<td>1 (3/127)</td>
<td>2.4%</td>
</tr>
<tr>
<td></td>
<td>Alopecia/Loss of small eyelash segment^{242,251}</td>
<td>2 (2/125)</td>
<td>1.1%-3%</td>
</tr>
<tr>
<td></td>
<td>Cellulitis^{251}</td>
<td>1 (2/92)</td>
<td>2.2%</td>
</tr>
<tr>
<td></td>
<td>Functional impairment^{251}</td>
<td>1 (2/92)</td>
<td>2.2%</td>
</tr>
</tbody>
</table>

IH = infantile hemangioma
No complications were noted in one study.^{247}
Discussion

State of the Literature

We identified 148 unique studies (15 randomized controlled trials [RCTs], 5 prospective and 19 retrospective cohort studies, 2 diagnostic accuracy studies, 1 study comparing pairs of treated and untreated infantile hemangioma (IH), and 106 case series) addressing our Key Questions. Forty-two comparative studies reported effectiveness outcomes (6 good quality, 22 fair quality, and 14 poor quality). One-hundred and forty-four studies (comparative studies and case series) reported harms/adverse events data (14 good quality for harms reporting, 3 fair quality, 127 poor quality). Eighty-one studies addressed beta-blockers (13 of which compared a beta-blocker to another category of intervention such as corticosteroids or laser); 26 addressed lasers; 24 addressed steroids; 15 addressed surgical approaches; and 2 addressed diagnostic modalities.

The literature on pharmacologic and surgical approaches for the treatment of 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 (though the mean age in this study was below 3 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=11/42 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 and surgical treatment (e.g., pulsed dye laser [PDL], argon laser, neodymium yttrium aluminum garnet [Nd:YAG] laser, cryotherapy) using varied regimens. Few (n=2) 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

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 of extracutaneous IH in children with multiple cutaneous lesions or with facial lesions in a beard distribution. Studies have primarily assessed associations between cutaneous IH and hepatic IH and cutaneous facial IH and airway IH.

Key Findings From Key (Comparative Effectiveness) Questions

Until fairly recently, corticosteroids were the treatment of choice for IH. As reported in this review, corticosteroids demonstrate some effectiveness but are 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, oral propranolol has been consistently shown to be superior in individual studies and in our network 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 typically to treat superficial IH, also reported greater effectiveness for timolol compared with placebo/observation in reducing IH lesion size, no differences in effects in one study comparing ophthalmic timolol and imiquimod; no differences in average overall improvement in another study comparing timolol and laser modalities; and greater response to timolol in superficial IH with greater response of mixed IH to timolol plus laser in a fourth study.

In our network meta-analysis specifically, the expected efficacy of control arms was estimated to be 6 percent (95% Bayesian credible interval [BCI]=1% to 11%). 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: 88% to 99%), followed by timolol (62%, 95% BCI: 39% to 83%) and intralesional triamcinolone (58%, 95% BCI: 22% to 93%), albeit with wider confidence bounds. Oral steroids had a clearance rate of 43 percent (95% BCI: 21% to 66%). The preponderance of available evidence used in the network 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 network meta-analysis below.

### KQ1. Effectiveness and Harms of Imaging

Two poor quality diagnostic accuracy studies addressed imaging modalities. 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 34) using weaker study designs and precluding a meta-analysis. The studies did not address harms.
Table 34. Strength of evidence for effectiveness of imaging modalities

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Outcome</th>
<th>Study Design</th>
<th>Consistency</th>
<th>Directness</th>
<th>Precision</th>
<th>Reporting Bias</th>
<th>Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRI vs. Ultrasound</td>
<td>Accuracy in detecting spinal anomalies</td>
<td>Cohort studies: 1 poor⁶⁸ (48)</td>
<td>High</td>
<td>Unknown</td>
<td>Direct</td>
<td>Imprecise</td>
<td>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.</td>
</tr>
<tr>
<td>MRI vs. Ultrasound vs. CT</td>
<td>Accuracy in detecting liver IH</td>
<td>Cohort studies: 1 poor⁷⁰ (55)</td>
<td>High</td>
<td>Unknown</td>
<td>Direct</td>
<td>Imprecise</td>
<td>NA Ultrasound detected lesions in 42/44 children (95% sensitivity). Insufficient SOE given single small, poor quality study.</td>
</tr>
</tbody>
</table>

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 24 studies (3 RCTs, 1 cohort study, and 20 case series) reporting outcomes and/or harms following corticosteroid use in children with IH.40,107-129,133 In addition, seven studies (described in the section on beta-blockers) compared beta-blockers and steroids.96-98,100,130-133 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 reporting lesion change data,108,122,252 140 had a “good” or “fair” response to steroids. In our network meta-analysis, oral steroids had a mean estimated expected clearance rate of 43 percent (95% BCI: 21% to 66%). Intraläsion triamcinolone had a rate of 58 percent but with wide confidence bounds (95% BCI: 22% to 93%).

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 intraläsional 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 35).
Table 35. Strength of evidence for effectiveness and harms of steroids

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Outcome</th>
<th>Study Design</th>
<th>Quality and Number of Studies (N Total)</th>
<th>Study Limitations</th>
<th>Consistency</th>
<th>Directness</th>
<th>Precision</th>
<th>Reporting Bias</th>
<th>Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral steroids vs. Observation or Placebo</td>
<td>Improvement in IH</td>
<td>Network meta-analysis</td>
<td>High</td>
<td>Consistent</td>
<td>Indirect</td>
<td>Imprecise</td>
<td>Undetected</td>
<td></td>
<td>In network meta-analysis oral steroids had a mean expected clearance rate of 43% (95% BCI: 21% to 66%) compared with 6% (95% BCI: 1% to 11%) for placebo/observation arms. Moderate SOE for greater effectiveness of oral steroids vs. placebo/observation given low precision and high study limitations.</td>
</tr>
<tr>
<td>Intralesional steroids vs. Observation or Placebo</td>
<td>Improvement in IH</td>
<td>Network meta-analysis</td>
<td>High</td>
<td>Consistent</td>
<td>Indirect</td>
<td>Imprecise</td>
<td>Undetected</td>
<td></td>
<td>In network meta-analysis intralesional steroids had a mean expected clearance rate of 58% (95% BCI: 22% to 99%) compared with 6% (95% BCI: 1% to 11%) for placebo/observation arms. Low SOE for greater effectiveness of intralesional steroids vs. placebo/observation given relatively small numbers of participants contributing to this comparison and low precision.</td>
</tr>
</tbody>
</table>
Table 35. Strength of evidence for effectiveness and harms of steroids (continued)

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Outcome</th>
<th>Study Design</th>
<th>Quality and Number of Studies (N Total)</th>
<th>Study Limitations</th>
<th>Consistency</th>
<th>Directness</th>
<th>Precision</th>
<th>Reporting Bias</th>
<th>Finding</th>
</tr>
</thead>
</table>
| All Steroids | Clinically important harms *(Cushingoid facies, growth retardation, mood changes /irritability, hypertension, infection)* | RCT: 2 good\(^98,107\) 1 poor\(^122\) (138)  
Cohort: 3 poor\(^40,96,97\) (179)  
Case series: 10 poor\(^109,110,112,113,115-117,120,129,133\) (2974) | High | Consistent | Direct | Precise | Undetected | Studies consistently reported these adverse effects.  
Moderate SOE for the association of steroids with clinically important harms due to high study limitations. |

BCI = bayesian credible interval; IH = infantile hemangioma; n = number; NA = not applicable; RCT = randomized, controlled trial; SOE = strength of evidence
Effectiveness and Harms of Beta-Blockers

Eighty-one studies (25 comparative studies and 56 case series) evaluated propranolol (oral, topical, intralesional), oral nadolol, oral atenolol, or timolol (topical gel or ophthalmic solution). Beta-blockers typically demonstrated significantly greater effects on reducing lesion size or volume than did control or other active comparators.

Compared with a mean estimated expected clearance rate of 6 percent (95% BCI: 1% to 11%) in placebo or observation arms, oral propranolol had a rate of 95 percent (95% BCI: 88% to 99%). With adequate data and precision, we considered the SOE to be high for the effect of oral propranolol on lesion size relative to observation or placebo arms. Individual studies assessed qualitatively typically 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 no difference in 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 36); SOE was insufficient for studies comparing timolol to other modalities including laser and imiquimod. Most studies of timolol included children with superficial lesions.
<table>
<thead>
<tr>
<th>Intervention</th>
<th>Outcome</th>
<th>Study Design</th>
<th>Quality and Number of Studies (N Total)</th>
<th>Study Limitations</th>
<th>Consistency</th>
<th>Directness</th>
<th>Precision</th>
<th>Reporting Bias</th>
<th>Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral propranolol vs. Placebo or Observation</td>
<td>Improvement in IH</td>
<td>Network meta-analysis</td>
<td>RCT: 2 good, (1^{17,92} 1) fair(^90) (510)</td>
<td>Low</td>
<td>Consistent</td>
<td>Indirect</td>
<td>Precise</td>
<td>Undetected</td>
<td>In network meta-analysis, the mean expected clearance rate for oral propranolol was 95% (95% BCI: 88% to 99%) relative to 6% (95% BCI: 1% to 11%) for placebo/observation arms; greater reductions in IH size in propranolol arms vs. control in all individual studies. High SOE for greater effectiveness of oral propranolol vs. placebo or observation based on individual comparisons and the network meta-analysis.</td>
</tr>
<tr>
<td>Rebound growth/Need for additional treatment</td>
<td></td>
<td>RCT: 1 good(^92) (456)</td>
<td>Cohort studies: 1 fair(^94) (45)</td>
<td>Low</td>
<td>Consistent</td>
<td>Direct</td>
<td>Precise</td>
<td>Undetected</td>
<td>Fewer than 15% of children in treatment arms had rebound growth or required longer/additional treatment. Moderate SOE for low level of rebound growth/need for further treatment associated with propranolol given few studies addressing the outcome.</td>
</tr>
<tr>
<td>Intervention</td>
<td>Outcome</td>
<td>Study Design Quality and Number of Studies (N Total)</td>
<td>Study Limitations</td>
<td>Consistency</td>
<td>Directness</td>
<td>Precision</td>
<td>Reporting Bias</td>
<td>Finding Strength of Evidence Grade</td>
<td></td>
</tr>
<tr>
<td>-----------------------------------</td>
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</tr>
<tr>
<td><strong>Oral propranolol vs. Steroids</strong></td>
<td><strong>Improvement in IH</strong></td>
<td>Network meta-analysis</td>
<td>High</td>
<td>Inconsistent</td>
<td>Indirect</td>
<td>Precise</td>
<td>Undetected</td>
<td>In head-to-head comparisons, propranolol more effective than oral steroids in 3 studies 96,97,132,133; two other studies reported no significant difference between oral or intralesional propranolol and oral or intralesional steroids 98,130. In a network meta-analysis, pooling data from multiple studies, propranolol was clearly superior to oral steroids (95% [95% BCI: 88% to 99%] clearance versus 43% [95% BCI: 21% to 66%] clearance). Moderate SOE for superiority of propranolol over steroids at achieving clearance based on combined effects from individual studies and network meta-analysis, high study limitations, and inconsistency...</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>RCT: 1 good96 (19)</td>
<td></td>
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<td></td>
<td>Insufficient SOE given single small study with high limitations.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cohort studies: 2 fair, 2 poor96,97,130,132,133 (216)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Significant size reductions from baseline in propranolol and combined arms (p values&lt;0.01) but not in prednisolone arm. Insufficient SOE given single small study with high limitations.</td>
<td></td>
</tr>
<tr>
<td><strong>Amblyopia</strong></td>
<td></td>
<td></td>
<td>High</td>
<td>Unknown</td>
<td>Direct</td>
<td>Imprecise</td>
<td>NA</td>
<td>No significant difference in level of amblyopia between oral propranolol and intralesional triamcinolone arms.</td>
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<tr>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Insufficient SOE given single small study with high limitations.</td>
<td></td>
</tr>
<tr>
<td><strong>Oral propranolol plus prednisolone vs. prednisolone vs. propranolol alone</strong></td>
<td><strong>Improvement in IH</strong></td>
<td>RCT: 1 fair100 (30)</td>
<td>High</td>
<td>Unknown</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Undetected</td>
<td></td>
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</tr>
</tbody>
</table>
Table 36. Strength of evidence for effectiveness of beta-blockers (continued)

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Outcome</th>
<th>Study Design</th>
<th>Study Limitations</th>
<th>Consistency</th>
<th>Directness</th>
<th>Precision</th>
<th>Reporting Bias</th>
<th>Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral propranolol vs. Other beta-blocker</td>
<td>Improvement in IH</td>
<td>RCT: 1 fair(^{102}) (23)</td>
<td>High</td>
<td>Consistent</td>
<td>Indirect</td>
<td>Imprecise</td>
<td>Undetected</td>
<td>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.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cohort studies: 1 fair, 1 poor(^{101,146-148}(77))</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Low SOE for no difference in response with propranolol, nadolol, or atenolol (systemic beta-blockers) based on few, small studies.</td>
</tr>
<tr>
<td>Oral propranolol vs. Intralesional bleomycin</td>
<td>Improvement in IH</td>
<td></td>
<td>High</td>
<td>Unknown</td>
<td>Direct</td>
<td>Imprecise</td>
<td>NA</td>
<td>No difference between agents in one small study.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cohort studies: 1 poor(^{95}(20))</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Insufficient SOE due to single study with high limitations.</td>
</tr>
<tr>
<td>Topical timolol vs. Placebo or Observation</td>
<td>Improvement in IH</td>
<td>Network meta-analysis</td>
<td>Medium</td>
<td>Consistent</td>
<td>Indirect</td>
<td>Precise</td>
<td>Undetected</td>
<td>Timolol more effective than placebo or observation in three comparative studies.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>RCT: 1 good(^{104}(41))</td>
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<td></td>
<td>In network meta-analysis, the mean expected clearance rate for topical timolol was 62% (95% BCI: 39% to 83%) relative to 6% (95% BCI: 1% to 11%) for placebo or observation arms.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cohort studies: 1 fair, 1 poor(^{103,144}(147))</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>Low SOE for effectiveness of timolol vs. placebo or observation based on medium study limitations and few studies.</td>
</tr>
</tbody>
</table>
### Table 36. Strength of evidence for effectiveness of beta-blockers (continued)

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Outcome</th>
<th>Study Design</th>
<th>Consistency</th>
<th>Directness</th>
<th>Precision</th>
<th>Reporting Bias</th>
<th>Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Topical timolol vs. timolol+PDL</td>
<td>Improvement in IH</td>
<td>Cohort studies: 1 poor(^1(^{106}) (102)</td>
<td>High</td>
<td>Unknown</td>
<td>Direct</td>
<td>Imprecise</td>
<td>NA</td>
</tr>
<tr>
<td>Topical timolol vs. PDL + Nd:YAG laser</td>
<td>Improvement in IH</td>
<td>RCT: 1 fair(^1(^4) (60)</td>
<td>High</td>
<td>Unknown</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Undetected</td>
</tr>
<tr>
<td>Topical timolol vs. Topical Imiquimod</td>
<td>Improvement in IH</td>
<td>Cohort studies: 1 fair(^1(^5) (38)</td>
<td>High</td>
<td>Unknown</td>
<td>Direct</td>
<td>Imprecise</td>
<td>NA</td>
</tr>
</tbody>
</table>

Timolol+PDL more effective than timolol alone (p=0.02). Insufficient SOE due to single study with high limitations.
Greater response to timolol among superficial IH and greater response to laser among mixed IH (p=NR).
Insufficient SOE due to single study with high limitations.

No significant differences in improvement in IH between groups. Insufficient SOE due to single study with high limitations.

BCI = bayesian credible interval; IH = infantile hemangioma; N = number; Nd:YAG = neodymium yttrium aluminum garnet; PDL = pulsed dye laser; 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=75/4872 children receiving beta-blockers [1.5%]) in case series and comparative studies). We considered the SOE to be moderate for the association of propranolol with clinically important and minor harms (Table 37).
<table>
<thead>
<tr>
<th>Intervention</th>
<th>Outcome</th>
<th>Study Design</th>
<th>Study Limitations</th>
<th>Consistency</th>
<th>Directness</th>
<th>Precision</th>
<th>Reporting Bias</th>
<th>Strength of Evidence Grade</th>
<th>Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral propranolol</td>
<td>Clinically important harms (hypotension, bradycardia, bronchospasm, hypoglycemia)</td>
<td>RCT: 2 good, 1 poor&lt;sup&gt;17,92,98&lt;/sup&gt; (515)</td>
<td>High</td>
<td>Consistent</td>
<td>Direct</td>
<td>Precise</td>
<td>Undetected</td>
<td>Moderate SOE for association of propranolol with these harms based on high study limitations.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cohort studies: 3 poor&lt;sup&gt;94,97,147&lt;/sup&gt; (213)</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Case series: 1 good, 15 poor&lt;sup&gt;16,153,171,172,185,190,191,193-195,199,200,202,203,205&lt;/sup&gt; (1249)</td>
<td></td>
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<tr>
<td>Minor harms (cold extremities, diarrhea, sleep changes)</td>
<td></td>
<td>RCT: 1 good, 3 poor&lt;sup&gt;17,92,98,100&lt;/sup&gt; (545)</td>
<td>High</td>
<td>Consistent</td>
<td>Direct</td>
<td>Precise</td>
<td>Undetected</td>
<td>Rates of these harms with propranolol ranged from 1% to 50% across studies.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cohort studies: 6 poor&lt;sup&gt;94,96,131,132,145,147&lt;/sup&gt; (270)</td>
<td></td>
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<td></td>
<td>Case series: 1 good, 12 poor&lt;sup&gt;16,171,172,185,189,191,193,195,200,202,203&lt;/sup&gt; (1140)</td>
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<tr>
<td>Intervention</td>
<td>Outcome</td>
<td>Study Design</td>
<td>Quality and Number of Studies (N Total)</td>
<td>Study Limitations</td>
<td>Consistency</td>
<td>Directness</td>
<td>Precision</td>
<td>Reporting Bias</td>
<td>Finding</td>
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<tr>
<td><strong>Timolol</strong></td>
<td><em>Lack of harms</em></td>
<td>RCT: 1 good, 1 poor(^{14,104}) (71)</td>
<td>Medium</td>
<td>Unknown</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Undetected</td>
<td>No harms observed with timolol in 5 comparative studies and 1 case series. Shortness of breath and insomnia observed in 1 of 30 children in one comparative study.(^{14})</td>
<td>Low SOE for lack of association of timolol with harms based on few studies.</td>
</tr>
<tr>
<td>Cohort studies: 1 good, 3 poor(^{103,105,106,144}) (287)</td>
<td>Case series: 1 poor(^{159}) (25)</td>
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<tr>
<td>Nadolol</td>
<td><em>Clinically important harms (hypotension, bradycardia, bronchospasm, hypoglycemia)</em></td>
<td></td>
<td>High</td>
<td>Unknown</td>
<td>Direct</td>
<td>Imprecise</td>
<td>NA</td>
<td>Harms of nadolol reported in 10%-20% of children. Insufficient SOE for association with clinically important harms given single, small poor quality cohort study.</td>
<td></td>
</tr>
<tr>
<td>Cohort studies: 1 poor(^{101}) (19)</td>
<td><em>Minor harms (cold extremities, diarrhea, sleep changes)</em></td>
<td>High</td>
<td>Unknown</td>
<td>Direct</td>
<td>Imprecise</td>
<td>NA</td>
<td>Harms of nadolol reported in 10%-50% of children. Insufficient SOE for association with minor harms given single, small poor quality study.</td>
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<tr>
<td>Intervention</td>
<td>Outcome</td>
<td>Study Design</td>
<td>Study Limitations</td>
<td>Consistency</td>
<td>Directness</td>
<td>Precision</td>
<td>Reporting Bias</td>
<td>Finding Strength of Evidence Grade</td>
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<tr>
<td>Atenolol</td>
<td>Hypotension</td>
<td>Cohort studies: 1 poor¹⁴⁷ (58)</td>
<td>High</td>
<td>Unknown</td>
<td>Direct</td>
<td>Imprecise</td>
<td>NA</td>
<td>Low SOE for the lack of association with minor harms given two small studies with high limitations.</td>
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<tr>
<td></td>
<td></td>
<td>RCT: 1 poor¹⁰² (23)</td>
<td>High</td>
<td>Consistent</td>
<td>direct</td>
<td>Imprecise</td>
<td>Undetected</td>
<td>Hypotension reported in 3% of children in one study.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Minor harms (cold extremities, diarrhea, sleep changes)</td>
<td>Cohort studies: 1 poor¹⁴⁷ (58)</td>
<td>High</td>
<td>Consistent</td>
<td>direct</td>
<td>Imprecise</td>
<td>Undetected</td>
<td>Insufficient SOE for association with hypotension given only a single, small poor quality study.</td>
<td></td>
</tr>
</tbody>
</table>

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 and Surgical Treatment

Eleven comparative studies (three RCTs, seven retrospective cohort studies, and one study that compared cryotherapy-treated and untreated IH pairs in individual children) addressed surgical approaches. In addition, one RCT and one cohort study (described in KQ2 above) compared topical timolol and laser modalities, and 28 case series addressed surgical approaches. Most comparative studies were small (≤55 participants), but one RCT and three retrospective cohort studies included more than 120 children. Lasers varied across studies in type, pulse width, or cooling materials. Most studies assessed variations of PDL (n=7) and examined heterogeneous endpoints. Most studies reported on treatment of cutaneous lesions.

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

Two comparative studies addressed surgical approaches (cryotherapy, intense pulsed light photothermolysis, sclerosis) and reported some positive effects in reducing IH size or improving appearance, but their smaller size and low quality preclude conclusions (insufficient SOE). Strength of evidence for outcomes after surgical treatments ranged from insufficient to low for effectiveness outcomes. The evidence was limited by low sample size, lack of comparisons of the same modalities, and variations in the laser settings used including wavelength and cooling protocols. For Nd:YAG and CO2 lasers, cryotherapy, and intense pulsed light photothermolysis, all studies were severely limited by sample size, and SOE was determined to be insufficient in all outcome parameters (Table 38).
Table 38. Strength of evidence for effectiveness of laser modalities

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Outcome</th>
<th>Study Design</th>
<th>Quality and Number of Studies (N Total)</th>
<th>Study Limitations</th>
<th>Consistency</th>
<th>Directness</th>
<th>Precision</th>
<th>Reporting Bias</th>
<th>Finding Strength of Evidence Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Longer pulse PDL vs. other laser types and protocols</td>
<td>Improvement in IH</td>
<td>RCT: 1 fair(^{211}) (52) Cohort studies: 2 poor(^{215,216}) (212)</td>
<td>Medium</td>
<td>Inconsistent</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Undetected</td>
<td>In 1 RCT, resolution outcomes similar between laser types; greater clearance in PDL +cooling arm in one cohort study(^{216}) and more children in PDL arm had complete regression than in Nd:YAG in another(^{215}); 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 longer pulse PDL and various other lasers given few studies, medium limitations, and inconsistent and imprecise findings.</td>
<td></td>
</tr>
<tr>
<td>PDL vs. Observation</td>
<td>Improvement in IH</td>
<td>RCT: 1 good, 1 fair(^{210,212}) (143)</td>
<td>Low</td>
<td>Consistent</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Suspected</td>
<td>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 improvement for PDL arm vs. observation in one study(^{210}). Low SOE for lack of difference between PDL treatment and observation in reducing lesion size due to lack of precision, few studies.</td>
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<tr>
<td>Intervention</td>
<td>Outcome</td>
<td>Study Design</td>
<td>Study Limitations</td>
<td>Consistency</td>
<td>Directness</td>
<td>Precision</td>
<td>Reporting Bias</td>
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<tr>
<td>PDL vs. Observation</td>
<td>Quality of life</td>
<td>RCT: 1 good, 1 fair</td>
<td>Medium</td>
<td>Inconsistent</td>
<td>Indirect</td>
<td>Imprecise</td>
<td>Undetected</td>
<td>No significant differences in parent ratings of QoL in one study; more parents of children in PDL arm in another considered appearance improved than in observation arm. Low SOE for lack of difference in QoL with PDL compared with observation due to lack of consistency and precision, few studies. Improved resolution with extended cooling protocol vs. traditional. Insufficient SOE given single study with medium limitations.</td>
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<tr>
<td>Nd:YAG with extended cooling vs. Nd:YAG with standard cooling</td>
<td>Improvement in IH</td>
<td>Cohort studies: 1 fair</td>
<td>Medium</td>
<td>Unknown</td>
<td>Direct</td>
<td>Imprecise</td>
<td>NA</td>
<td>Improved resolution with extended cooling protocol vs. traditional. Insufficient SOE given single study with medium limitations.</td>
<td></td>
</tr>
<tr>
<td>Nd:YAG vs. CO₂ laser vs. Tracheostomy</td>
<td>Speech</td>
<td>Cohort studies: 1 poor</td>
<td>High</td>
<td>Unknown</td>
<td>Indirect</td>
<td>Imprecise</td>
<td>NA</td>
<td>75% of children with tracheostomy had delayed speech vs. 0 with no tracheostomy in the laser treatment era. Insufficient SOE given small, single study.</td>
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<tr>
<td>Intervention</td>
<td>Outcome</td>
<td>Study Design</td>
<td>Study Limitations</td>
<td>Consistency</td>
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<tr>
<td>Cryotherapy vs. Observation</td>
<td>Improvement in IH</td>
<td>Comparative study with treated/untreated IH per child: 1 poor(^220) (13)</td>
<td>High</td>
<td>Unknown</td>
<td>Direct</td>
<td>Imprecise</td>
<td>NA</td>
<td>76% of IH in treated arm vs. 12% in untreated resolved without scarring. Insufficient SOE given single, small study with high limitations.</td>
<td></td>
</tr>
<tr>
<td>Photo-thermolysis with Intense Pulsed Light With or Without Sclerosis vs. Cryotherapy</td>
<td>Improvement in IH</td>
<td>Cohort studies: 1 poor(^219) (250)</td>
<td>High</td>
<td>Unknown</td>
<td>Direct</td>
<td>Imprecise</td>
<td>NA</td>
<td>More children had ≥50% reduction in IH size in the combined therapy arm than in other arms (p=NR). Insufficient SOE given single study with high limitations.</td>
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</tbody>
</table>

CO\(_2\) = carbon dioxide; IH = infantile hemangioma; NA = not applicable; NR = not reported; Nd:YAG = neodymium 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 and scarring after cryotherapy.

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. 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 (Table 39).
Table 39. Strength of evidence for harms of laser modalities

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Outcome</th>
<th>Study Design</th>
<th>Quality and Number of Studies (N Total)</th>
<th>Study Limitations</th>
<th>Consistency</th>
<th>Directness</th>
<th>Precision</th>
<th>Reporting Bias</th>
<th>Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>PDL</td>
<td><strong>Pigmentation changes</strong></td>
<td>RCT: 1 good</td>
<td>1 good, 1 poor²¹¹,²¹² (173)</td>
<td>Low</td>
<td>Consistent</td>
<td>Direct</td>
<td>Precise</td>
<td>Undetected</td>
<td>Hypo- or hyper-pigmentation consistently reported, with hypopigmentation reported more frequently.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cohort studies: 1 good, 1 poor²¹³,²¹⁵ (73)</td>
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<td>Moderate SOE for association of PDL with skin pigmentation complications based on relatively few participants in studies.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Case series: 1 fair, 4 poor²²¹,²²²,²²₅,²²₈,²³₀ (1017)</td>
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<tr>
<td></td>
<td><strong>Bleeding</strong></td>
<td>RCT: 1 good</td>
<td>²¹² (121)</td>
<td>Low</td>
<td>Unknown</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Undetected</td>
<td>No significant difference in bleeding between short pulse PDL and observation groups.</td>
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<td>Low SOE for association of bleeding with PDL based on one study with low limitations, unknown consistency, and imprecision.</td>
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<tr>
<td></td>
<td><strong>Pain</strong></td>
<td>RCT: 1 good</td>
<td>²¹² (121)</td>
<td>Low</td>
<td>Unknown</td>
<td>Indirect</td>
<td>Imprecise</td>
<td>Undetected</td>
<td>13% of parents reported pain for their children after PDL.</td>
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<td>Insufficient SOE for pain following PDL given few occurrences of outcome. Pain is also difficult to assess in infant population.</td>
</tr>
<tr>
<td></td>
<td><strong>Scarring</strong></td>
<td>Cohort studies: 1 good²¹⁵ (50)</td>
<td></td>
<td>Medium</td>
<td>Inconsistent</td>
<td>Direct</td>
<td>Imprecise</td>
<td>NA</td>
<td>1/25 children receiving PDL in one study 7/769 children in case series had scarring.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Case series: 2 fair, 1 poor²²⁷,²²₈,²₃₀ (769)</td>
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<td>Insufficient SOE due to few occurrences of the outcome reported in studies.</td>
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<tr>
<td>Intervention</td>
<td>Outcome</td>
<td>Study Design</td>
<td>Quality and Number of Studies (N Total)</td>
<td>Study Limitations</td>
<td>Consistency</td>
<td>Directness</td>
<td>Precision</td>
<td>Reporting Bias</td>
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<tr>
<td>Nd:YAG</td>
<td>Pigmentation changes</td>
<td>Cohort studies: 1 good(^{215}) (50)</td>
<td>Low</td>
<td>Unknown</td>
<td>Direct</td>
<td>Imprecise</td>
<td>NA</td>
<td>2/25 children receiving Nd:YAG in one study had scarring. Insufficient SOE due to few occurrences of the outcome reported.</td>
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<tr>
<td></td>
<td>Scarring</td>
<td>Cohort studies: 1 good, 2 poor(^{214,215,218}) (386)</td>
<td>Medium</td>
<td>Consistent</td>
<td>Direct</td>
<td>Precise</td>
<td>NA</td>
<td>Most studies reported scarring in ≤5% of children. Low SOE for association of scarring with Nd:YAG treatment due to few occurrences of the outcome reported.</td>
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<tr>
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<td>Case series: 3 poor(^{231,232,234}) (954)</td>
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<tr>
<td></td>
<td>Bleeding</td>
<td>Case series: 2 poor(^{232,234}) (794)</td>
<td>High</td>
<td>Unknown</td>
<td>Direct</td>
<td>Precise</td>
<td>Undetected</td>
<td>Bleeding noted in 13/794 children. Insufficient SOE due to few occurrences of the outcome reported in studies.</td>
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<tr>
<td>Cryotherapy vs. Observation</td>
<td>Scarring</td>
<td>Comparative study with treated/untreated IH per child: 1 poor(^{220}) (13)</td>
<td>High</td>
<td>Unknown</td>
<td>Direct</td>
<td>Imprecise</td>
<td>NA</td>
<td>Scarring in 4 of 17 IH treated with cryotherapy. Insufficient SOE due to single, small study.</td>
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<tr>
<td>Intervention</td>
<td>Outcome</td>
<td>Study Design</td>
<td>Consistency</td>
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<td>Reporting Bias</td>
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<tr>
<td>Surgical Excision or Resection</td>
<td><strong>Scarring</strong>&lt;br&gt;Case series: 2 poor&lt;sup&gt;249,251&lt;/sup&gt; (142)</td>
<td>High</td>
<td>Consistent</td>
<td>Direct</td>
<td>Imprecise</td>
<td>NA</td>
<td>Scarring in 11/192 children. Insufficient SOE due to few occurrences of the outcome reported in studies.</td>
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<td></td>
<td><strong>Wound dehiscence</strong>&lt;br&gt;Case series: 7 poor&lt;sup&gt;238,240,241,243,246,248,251&lt;/sup&gt; (483)</td>
<td>High</td>
<td>Consistent</td>
<td>Direct</td>
<td>Imprecise</td>
<td>NA</td>
<td>Dehiscences in 20/483 children. Insufficient SOE due to few occurrences of the outcome reported in studies with high limitations.</td>
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</table>

IH = infantile hemangioma; 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
Findings in Relation to What is Already Known

We identified ten recent (2010-present) systematic review or meta-analyses assessing interventions for IH. Most reviews addressed propranolol or beta-blockers: three addressed propranolol generally; two examined effectiveness specifically for airway IH; one for periocular IH; and two compared beta-blockers and steroids. One Cochrane review assessed multiple interventions, and two additional reviews examined intralesional steroids and laser treatment.

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).

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).

Applicability

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

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

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

Studies addressing steroids compared various routes of steroid administration (oral, topical, and intralesional) and various agents (methylprednisolone, triamcinolone, mometasone furoate) in children with ages ranging from less than 1 to 72 months. Studies likely included children with IH in the proliferative and involution phase, which may limit applicability to younger or
older children. One comparative study was conducted in Canada and the others in Turkey, Pakistan, and India. Applicability may be limited given differences in the systems of care in these lower resource countries. Comparative studies were also published between 2001 and 2014 and may not fully represent evolutions in standards of care.

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

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

Newer lasers and adjunctive features such as dynamic cooling have resulted in older lasers being out of date, thus limiting the applicability of studies conducted with those models. Most laser studies evaluated lasers as first-line treatment, which is currently less common in practice since the advent of beta-blocker treatment in countries, like the United States, where such treatments are readily available, as beta-blockers have generally superseded other treatments as first-line management of IH. Additionally, most comparative literature evaluated PDL, which is typically used only for the treatment of superficial lesions. 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 agent 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 [95% BCI: 88% to 99%] and 62% for topical timolol [95% BCI: 39% to 83%], compared with 6% for observation/placebo arms [95% BCI: 1% to 11%]).

Steroids were associated with mean expected clearance rates of 43 percent (95% BCI: 21% to 66%) for oral steroids and 58 percent (95% BCI: 22% to 99%) for intralesional triamcinolone in our network 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). 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 little 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 and did not seek or include unpublished data. 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. While this undoubtedly means that some treatment outcomes are not included in this review, these drugs are not frequently used since the advent of beta-blocker treatment for IH in the opinion of our clinical experts.

We also used only comparative studies to address questions of effectiveness and case series with at least 25 participants to provide harms data. These requirements eliminated some smaller
case series reporting on rarer presentations of IH (e.g., liver IH). We were also dependent upon
the characterization of IH as presented in each study. Given changes in nomenclature and
variations in the way IH are described, it may be that some studies included non-IH lesions.
However, our clinical experts carefully reviewed studies to attempt to ascertain that included
studies were reporting on true IH. We also note that other approaches to meta-analysis could be
used, but that our estimates of a high anticipated response to propranolol largely align with those
in other reviews of propranolol.254,258,259,261

Limitations of the Evidence Base

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

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

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

The most important deficiency in the reported outcomes across studies is the tendency for the
reporting of discretized outcomes, when the underlying outcome is a continuous variable.
Specifically, though outcomes are likely recorded as a continuous measure (i.e., the proportion of
an existing lesion that is cleared or reduced in size following treatment), authors often chose an
arbitrary cutoff proportion (or a small number of bins) and reported only the numbers in each of
the resulting categories. This results in an immediate and unrecoverable loss in power for any
quantitative meta-analyses. Researchers should be encouraged to report outcome variables as
they were recorded, without transforming them in such a way that information is lost. In
addition, methods for measurement of outcomes such as rebound growth are not clearly reported;
thus, our understanding of the magnitude of regrowth is limited.
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. In general, imaging is infrequently used to differentiate accurately an IH from other vascular lesions. When a diagnosis is in question, a tissue biopsy is the most accurate method to determine the diagnosis. Future studies should use imaging modalities at the same point in the IH course to allow direct comparison. Studies should also report adverse effects of imaging, which are not addressed in the literature meeting criteria for this review.

- **Indications for treatment and treatment referral.** While it is likely that non-placebo-controlled studies reviewed here included mostly children with problematic IH (e.g., lesions that are vision-threatening or disfiguring, ulcerated lesions, airway/life-threatening lesions), studies did not always clearly report indications for treatment or referral for treatment. Children may be referred for life-, functional-, or vision-threatening reasons, but in the beta-blocker era, potential disfigurement is likely a cause for referral.

- **Appropriate dosing for propranolol and timing of treatment.** The largest RCT to date 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 as well as effects on cognition, memory, and the central nervous system are not well-understood in the population of very young children receiving beta-blockers for IH.

- **Treatment choice for specific lesion types and locations.** Characteristics, such as lesion size, location, and persistence, as well as modifiers such as patient age, functional impact, and IH subtype influence whether children are treated with pharmacologic agents or surgically. Lesion characteristics also influence the choice of specific pharmacologic agents. Most studies included multiple lesion types and in multiple locations, and few included specific modifier analyses or reported outcomes by lesion characteristics. Research to improve understanding of which lesions are likely to respond best to specific
agents is critical, especially as understanding of the effectiveness of beta-blockers in the involution phase is limited. Optimal treatment in the proliferative phase may be key to maximal resolution of IH.

- **Assessment of methods for assessing rebound growth.** A number of studies reported regrowth of lesions but typically did not indicate what constituted rebound growth. Greater clarity in reporting this outcome would help to clarify our understanding of effectiveness.

- **Characteristics that may influence response to beta-blockers.** Studies of beta-blockers were typically not powered to provide information on subgroups, but a percentage of children did not respond or responded minimally to propranolol. In 10 comparative studies of beta-blockers reporting these data, \(17,93,94,98,103,104,130,144,146,147,150\) 20 percent of children (n=63/314) had a limited or no response to the agent. We lack data to assess whether improvement in lesions or promotion of involution is affected by child age or number, severity, type, or anatomic location of lesions. Similarly, understanding the mechanisms of growth of IH will promote our understanding of response to treatments and treatment safety.

- **Use of beta-blockers other than propranolol.** Small cohort studies of oral atenolol and nadolol and topical or ophthalmic timolol showed positive effects on IH resolution with few side effects. Additional RCTs of these agents, with clear reporting of lesion parameters and child characteristics, would increase our understanding of their effectiveness and comparative effectiveness versus propranolol.

- **Treatments for hepatic IH.** Few treatment studies explicitly reported if children had hepatic IH. Most studies included children with IH in multiple locations, so children could have had hepatic IH as well; however, the applicability of findings to children with visceral IH is not clear.

- **Use of steroids and laser treatments in the beta-blocker era.** Clinical practice in the United States is moving toward use of a beta-blocker as the first-line treatment for IH;\(^{15}\) however, a number of recent studies report use of steroids and laser treatments in younger children with lesions in the proliferative stage. Given the side effect profile of steroids, understanding of whether or when to use such agents in the absence of life-threatening lesions or contraindications to beta-blockers is needed. Current literature does not provide sufficient data to address these questions.

- **Interventions to follow beta-blockers or corticosteroids if such treatments fail.** We did not identify any studies that clearly reported data on this question. While most children receiving beta-blockers in the studies reviewed here responded to the medication, some had no or minimal response.

- **Standardization of scoring tools to assess change in IH.** IH outcomes are necessarily assessed using subjective measures, and investigators typically reported grading scales used to assess change in IH size or appearance. Few studies, however, commented on interrater reliability of instruments. Research to improve standardization among tools and the development of uniform scoring systems and measurements would improve our ability to combine outcomes across studies.

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

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


Abbreviations and Acronyms Used in This Report

AHRQ  Agency for Healthcare Research and Quality
BCI  Bayesian Credible Interval
CER  Comparative Effectiveness Review
CI  Confidence Interval
cm  Centimeters
CO₂  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
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
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<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>US</td>
<td>Ultrasound</td>
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<tr>
<td>VAS</td>
<td>Visual Analog Scale</td>
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# Appendix A. Search Strategies

## Searches for Contextual Questions

### Table A-1. MEDLINE (PubMed)

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<td>897</td>
</tr>
<tr>
<td>#6 #5 AND Humans[mh]</td>
<td>892</td>
</tr>
</tbody>
</table>

Key: [mh] medical subject heading; [nm] supplementary concept; [tiab] keyword in title or abstract; [la] language; [pt] publication type; [sh] subheading

### Table A-2. CINAHL search strategies (EBSCO Host interface)

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<tr>
<th>Search Terms</th>
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</thead>
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<td>#1 (MH “Hemangioma”) OR (MH “Hemangioma, Cavernous”) OR “infantile hemangioma” OR “infantile hemangiomas” OR “infantile haemangiomas” OR “IH”</td>
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</tr>
<tr>
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<td>452</td>
</tr>
<tr>
<td>#4 S3 AND limiters: English language</td>
<td>449</td>
</tr>
<tr>
<td>#5 S4 AND limiters: Exclude MEDLINE records</td>
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</tr>
</tbody>
</table>

Key: MH CINAHL medical subject heading; MW CINAHL subheading
Table A-3. EMBASE search strategies (OvidSP interface)

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<th>Search Terms</th>
<th>Search Results</th>
</tr>
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<td>#1 Capillary hemangioma / or infantile hemangioma.tw. or infantile hemangiomas.tw. or infantile haemangioma.tw. or infantile haemangiomas.tw. or haemangioma.tw. or hemangiomas.tw. or IH.tw.</td>
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<tr>
<td>#5 Limit 4 to human</td>
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<tr>
<td>#6 5 not (editorial.pt. or letter.pt. or note.pt. or short survey.pt. or conference paper.pt.)</td>
<td>3155</td>
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Key: / Emtree heading; .tw. abstract, title and drug trade name; /cn congenital; .fs. subheading; si.fs. side effects subheading; th.fs. therapy subheading; su.fs. surgery subheading; co.fs. complications subheading; pt. publication type
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<tr>
<td>#7</td>
<td>#6 AND (“1982/01/01”[Date - Publication] : “3000”[Date - Publication])</td>
<td>4358</td>
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</table>

Key: [mh] medical subject heading; [nm] supplementary concept; [tiab] keyword in title or abstract; [la] language; [pt] publication type; [sh] subheading
### Table A-5. CINAHL search strategies (EBSCO Host interface)

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<td>#1 (MH “Hemangioma”) OR (MH “Hemangioma, Cavernous”) OR “infantile hemangioma” OR “infantile hemangiomas” OR “infantile haemangiomas” OR “IH”</td>
<td>1,163</td>
</tr>
<tr>
<td>#2 (MH “Infant, Newborn, Diseases”) OR (MH “Infant”) OR (MH “Infant, Newborn”) OR “infant” OR “infants” OR “infantile” OR “newborn” OR “pediatric” OR “neonat*” OR (MH “Child”) OR “child” OR “children”</td>
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</table>

Key: MH CINAHL medical subject heading; MW CINAHL subheading

### Table A-6. EMBASE search strategies (OvidSP interface)

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Key: / Emtree heading; .tw. abstract, title and drug trade name; /cn congenital; .fs. subheading; si.fs. side effects subheading; th.fs. therapy subheading; su.fs. surgery subheading; co.fs. complications subheading; pt. publication type
Appendix B. Screening and Quality Assessment Forms

Infantile Hemangioma Abstract Review Form

1. Does this reference include an abstract?
   □ Yes □ No □ Cannot Determine

2. Does this study include newborns, infants or children (ages 0-18) with diagnosis of infantile hemangioma (or suspected hemangioma)?
   (Do not include hemangioblastomas, hemangioendothelioma, cavernous hemangiomas/lesions/malformation, non-involuting congenital hemangiomas (NICH), rapid involuting congenital hemangiomas (RICH), vascular malformations, choroidal hemangiomas, diffuse hemangiomatosis, angiomas, verrucous hemangiomas)
   □ Yes □ No □ Cannot Determine

3. Is this study original research (e.g., not commentaries, literature reviews, or systematic reviews, letters to the editor, editorials, case reports)?
   □ Yes □ No □ Cannot Determine

4. Does this study address the effectiveness or harms of a diagnostic modality or surgical, laser or pharmacological intervention for infantile hemangioma?
   □ Yes □ No □ Cannot Determine

   **Diagnostic modality/workup evaluation Including but not limited to:**
   Diagnostic imaging including MRI, CT, MRA, Echo, Ultrasound

   **Surgical interventions Including but not limited to:** cryotherapy, resection, embolization, radiofrequency ablation therapy, incisional biopsy

   **Laser treatment Including but not limited to:**
   Pulsed dye, fractionated, argon, carbon dioxide, neodymium (Nd): YAG, Erbium lasers

   **Pharmacologic interventions Including but not limited to:**
   Beta-blockers (e.g., systemic propranolol, topical timolol); corticosteroids (topical, intralesional, systemic); sirolimus, imiquimod, interferon, bleomycin, vincristine, ACE inhibitors, antiangiogenic agents

5. Does this article address contextual questions including natural history, adverse outcomes of untreated infantile hemangioma, characteristics of the hemangioma that indicate risk of significant medical complications that would prompt immediate medical or surgical intervention, or evidence for the association of multiple cutaneous hemangiomas and increased risk of occult hemangiomas?
   □ Yes □ No □ Cannot Determine

   **Retain for:**
   □ Background/Discussion □ Review of References □ Other: ____________________

   **Comments:**
Infantile Hemangioma Full Text Review Form

1. Eligible study design:
   □ RCT
   □ Cohort study with comparison group
   □ Case-control
   □ Case series reporting harms and including at least 25 children with IH
   □ Case series with <25 children with IH
   □ None of the above

2. N participants:
   ______________________

3. Study informs a key question:
   □ KQ1: Benefits/harms of imaging
   □ KQ2: Benefits/harms of corticosteroids/beta-blockers
   □ KQ3: Benefits/harms of second-line therapies after corticosteroids/beta-blockers
   □ KQ4: Benefits/harms of surgery/laser
   □ Other: Benefits/harms of second-line after no or other drugs
   □ Does not address a KQ

4. Please list intervention:
   ______________________

5. Does this study include baseline and follow-up data for an outcome of interest?
   □ Yes, baseline and follow-up
   □ No, follow-up/final data only

6. Retain for:
   □ Background/Discussion □ Review of references □ Contextual questions

7. Comments:
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<tbody>
<tr>
<td>1. Are any important harms or adverse events that may be a consequence of the intervention/exposure missing from the results? (RTI cohort)</td>
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<td>2. Were the harms predefined using standardized or precise definitions? (mcharms)</td>
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<td>Pre-defined indicates that the harms that were expected are explicitly defined prior to the collection of these expected events. For example, if bleeding is listed as a harmful event, the criteria by which they determine the bleeding (i.e. body location, type, or amount of blood loss that counts as an event, etc) should be specified. Standardized classification of harms can be derived from any of the following: 1) reference to standard terminology or classifications of harms from a recognized external organization(s) such as government regulatory or health agencies. Examples of standardized terminology for harms includes, WHO-ART, MEDra, HTA report on the Measurement and Monitoring of Surgical Adverse Events) 2) previously explicitly defined classifications of harms in the literature, or 3) based on pre-specified clinical criteria, or 4) pre-specified laboratory test (may not need to have a specific cut-off level specified in all cases) In some instances only some of the harms identified in a study will be precisely defined. In this case, there must be some judgement if the nature of the harms not pre-defined.</td>
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<td>3. Are all pre-specified harms reported? (RTI case series)</td>
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<td>IF #2 is NO, this is unclear</td>
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<td>4. Did the author(s) use STANDARD scale(s) or checklist(s) for harms collection? (mcharms)</td>
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**Standard scales or checklists are those that have at least one of the following:**
- Established reliability and validity (specified in the text);
- Are very widely used within the discipline (may have to check the reference list for the scale).

In the instance where the methods indicate that a **NEW** scale or checklist was developed for the study specifically, the author(s) must explicitly specify the CONTENT of the new scale or checklist in sufficient detail (for example, the body systems evaluated, or the specific tests or questions included.)

| 5. | Are the statistical methods used to assess the main harm or adverse event outcomes adequate? (RTI cohort) |

Note: This form derived from questions from the RTI Item bank and McHarms tool.
Good= 4-5 "yes"; Fair=3 “yes” out of 5; Poor=2 “yes” or less
### QUADAS Diagnostic Accuracy Rating Tool – For Diagnosis studies Form

<table>
<thead>
<tr>
<th></th>
<th>Question</th>
<th>Yes</th>
<th>No</th>
<th>Unclear</th>
<th>Comments</th>
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<tr>
<td>1</td>
<td>Was the spectrum of patients representative of the patients who will receive the test in practice?</td>
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<td>2</td>
<td>Were selection criteria clearly described?</td>
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<td>3</td>
<td>Is the reference standard likely to correctly classify the target condition?</td>
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<td>4</td>
<td>Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests?</td>
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<td>5</td>
<td>Did the whole sample or a random selection of the sample, receive verification using a reference standard of diagnosis?</td>
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<td>6</td>
<td>Did patients receive the same reference standard regardless of the index test result?</td>
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<td>7</td>
<td>Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)?</td>
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<td>8</td>
<td>Was the execution of the index test described in sufficient detail to permit replication of the test?</td>
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<td>9</td>
<td>Was the execution of the reference standard described in sufficient detail to permit its replication?</td>
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<td>10</td>
<td>Were the index test results interpreted without knowledge of the results of the reference standard?</td>
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<td>11</td>
<td>Were the reference standard results interpreted without knowledge of the results of the index test?</td>
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<tr>
<td>12</td>
<td>Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?</td>
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<tr>
<td>13</td>
<td>Were uninterpretable/intermediate test results reported?</td>
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<tr>
<td>14</td>
<td>Were withdrawals from the study explained?</td>
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</table>
Newcastle-Ottawa Quality Assessment Form for Cohort Studies Form

Note: A study can be given a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability.

REFID:___________________ Reviewer:________________

Selection
1) Representativeness of the exposed cohort:
   a) Truly representative (one star)
   b) Somewhat representative (one star)
   c) Selected group
   d) No description of the derivation of the cohort

2) Selection of the non-exposed cohort
   a) Drawn from the same community as the exposed cohort (one star)
   b) Drawn from a different source
   c) No description of the derivation of the non exposed cohort

3) Ascertainment of exposure:
   a) Secure record (e.g., surgical record) (one star)
   b) Structured interview (one star)
   c) Written self report
   d) No description
   e) Other

4) Demonstration that outcome of interest was not present at start of study:
   a) Yes (one star)
   b) No

Comparability
5) Comparability of cohorts on the basis of the design or analysis controlled for confounders:
   a) The study controls for age (one star)
   b) Study controls for other factors (list) _________________________________ (one star)
   c) Cohorts are not comparable on the basis of the design or analysis controlled for confounders

Outcome
6) Assessment of outcome:
   a) Independent blind assessment (one star)
   b) Record linkage (one star)
   c) Self report
   d) No description
   e) Other

7) Was follow-up long enough for outcomes to occur:
   a) Yes (one star)
   b) No

   Indicate the median duration of follow-up and a brief rationale for the assessment above:____________________

8) Adequacy of follow-up of cohorts:
   a) Complete follow up- all subject accounted for (one star)
   b) Subjects lost to follow up unlikely to introduce bias- number lost less than or equal to 20% or description of those lost suggested no different from those followed. (one star)
   c) Follow up rate greater than 80% and no description of those lost
   d) No statement

9) Would answers to any of these questions vary based on the specific outcome assessed? If yes, please explain:

_____________________________________________________________________________________________
_____________________________________________________________________________________________
## Infantile Hemangioma CER: Risk of Bias for RCTs Form
**Reviewer Initials: _____ Ref ID: __________**

<table>
<thead>
<tr>
<th>Risk of Bias</th>
<th>Criterion</th>
<th>Yes</th>
<th>No</th>
<th>Unclear</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selection bias</td>
<td>Was the allocation sequence generated adequately (e.g., random number table, computer-generated randomization)?</td>
<td></td>
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<td>Was the allocation of treatment adequately concealed (e.g., pharmacy-controlled randomization or use of sequentially numbered sealed envelopes)?</td>
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<td>Were participants analyzed within the groups they were originally assigned to?</td>
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<td></td>
<td>Does the design or analysis control account for important confounding and modifying variables through matching, stratification, multivariable analysis, or other approaches?</td>
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<td>Performance bias</td>
<td>Did researchers rule out any impact from a concurrent intervention or an unintended exposure that might bias results?</td>
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<td></td>
<td>Did the study maintain fidelity to the intervention protocol?</td>
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<td>Attrition bias</td>
<td>If attrition (overall or differential nonresponse, dropout, loss to follow-up, or exclusion of participants) was a concern, were missing data handled appropriately (e.g., intention-to-treat analysis and imputation)?</td>
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<td>Detection bias</td>
<td>Was the length of follow-up different between the groups?</td>
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<td></td>
<td>Were the outcome assessors blinded to the intervention or exposure status of participants?</td>
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<td></td>
<td>Were interventions/exposures assessed/defined using clearly defined measures, implemented consistently across all study participants?</td>
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<td></td>
<td>Were outcomes assessed using clearly defined measures, implemented consistently across all study participants?</td>
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<td>Reporting bias</td>
<td>Were the potential outcomes prespecified by the researchers?</td>
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<td>Are all prespecified outcomes reported?</td>
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<tr>
<td>Other</td>
<td>List outcomes of interest assessed:</td>
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<td></td>
<td>Would answers to any of these questions vary by the specific outcome assessed? If yes, please explain in Comments box.</td>
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### OUTCOMES OF INTEREST FOR REVIEW

**Imaging:** Ability to identify presence, number, and extent of hemangiomas and associated structural anomalies (sensitivity and specificity)

**Treatment:** Size / volume of hemangioma; Impact on vision; Aesthetic appearance as assessed by clinician or parent; Degree of ulceration; Quality of life
## Appendix C. Excluded Studies

### Reasons for Exclusion
- **X-1** Does not include children with infantile hemangioma
- **X-2** Not original research
- **X-3** Does not address interventions/outcomes of interest
- **X-4** Ineligible study design
- **X-5** Not obtainable
- **X-6** Not in English


C-14


628. van der Stricht J. The sclerotherapy therapy in congenital vascular defects. Int Angiol. 1990 Jul-Sep;9(3):224-7. PMID: 2097076; X-1


885. Sheehan-Dare RA. Laser treatment of port wine stains. BMJ. 1993 Feb 6;306(6874):394-5. PMID: 8461702; X-1


1001. Drigo P, Battistella PA, Mammi I. Familial cerebral, hepatic, and retinal cavernous angiomas. Childs Nerv Syst. 1995 Feb;11(2):65. PMID: 7758014; X-1


1251. Wheeler HMD. Clinical issues in midwifery. Birthmarks, body image and their implications... this article is the first in a series of three. Br J Midwifery. 1997;5(5):272-6. PMID: X-1


1416. Robinson HA, Keeton BR, Moore IE. Critical obstruction of the right ventricular outflow tract by a primary hemangioendothelioma in a seven month old. Cardiol Young. 1999 Mar;9(2):185-8. PMID: 10323517; X-1


C-66


1509. Prayson RA. Clinicopathological findings in patients who have undergone epilepsy surgery in the first year of life. Pathol Int. 2000 Aug;50(8):620-5. PMID: 10972860; X-1


1604. McDonald HR. Diagnostic and therapeutic challenges. Retina. 2001;21(1):62-4; discussion 4-5. PMID: 11217932; X-1


1856. Skorin L, Jr. Photo quiz: can you identify these facial findings? Consultant. 2003;43(10):1245–6, 50, 53 passim. PMID: X-1


1898. Blereau RP. Do you recognize these disorders? Consultant. 2004 01 Apr;44(4):605-10. PMID: 2005087462; X-1


1917. Fogelholm R. Ionising radiation in infancy and adult cognitive function: radiation may not solely explain later cognitive function. BMJ. 2004 Mar 6;328(7439):581-2; author reply 2. PMID: 15001513; X-1


1962. Prabhu SP. Ionising radiation in infancy and adult cognitive function: wrong impression was created by study's publicity. BMJ. 2004 Mar 6;328(7439):582; author reply PMID: 15001515; X-1


2013. Borsaru AD, Naidoo P. Pyogenic abscess complicating a resolving cerebral haematoma secondary to a cavernous haemangioma: computed tomography and magnetic resonance imaging findings. Austr alas Radiol. 2005 Apr;49(2):144-50. PMID: 15845053; X-1


2137. Woo CLF, Ho BHT, Young BWY. A newborn with ptosis secondary to a cavernous haemangioma. Hong Kong Journal of Paediatrics. 2005 July;10(3):211-3+8. PMID: 2005382991; X-1


2164. Cong X. Kangaroo care for analgesia in preterm infants undergoing heel stick pain: Case Western Reserve University; 2006.


Morota N, Deletis V. The importance of brainstem mapping in brainstem surgical anatomy before the fourth ventricle and implication for intraoperative neurophysiological mapping. Acta Neurochir (Wien). 2006 May;148(5):499-509; discussion PMID: 16374568; X-1


2252. Shroff PK, Martin TW, Schmitz ML. Successful anesthetic management of a child with an extensive facial hemangioma and high output cardiac failure for placement of a central venous catheter. Paediatr Anaesth. 2006 Jan;16(1):77-81. PMID: 16409535; X-2


2268. Tekkok IH, Sav A. Supratentorial cystic hemangioblastoma with infiltrantorial extension—a unique location and a rare infant case. Childs Nerv Syst. 2006 Sep;22(9):1177-81. PMID: 16534645; X-1


2304. Barankin B. Dermatology case challenge: what is the lesion on this infant's face? Patient Care. 2007;41:2p. PMID: X-1


2323. Coats D, Paysse EA. Orbital hemangioma. Ophthalmology. 2007 Dec;114(12):2369. PMID: 18054658; X-3, X-4


2511. Ho R. Hail to the red, white, and blue! Contemp Pediatr. 2008;25(9):51. PMID: X-1


2622. CME posttest. JAAPA. 2009;22(5):50-. PMID: X-1


2854. Crouch M. As they grow: 0-12 months. Taking care of it! Parents. 2010;85(7):152. PMID: X-1


2965. Peterson JD, Friedman PM. Letter regarding early laser treatment of periorbital infantile hemangiomas may work, but is it really the best treatment option? Dermatol Surg. 2010 Sep;36(9):1497-8. PMID: 21413192; X-3, X-4


2996. Suh KY, Frieden IJ. Infantile haemangiomas with minimal or arrested growth: a retrospective case series. Arch Dermatol. 2010 Sep;146(9):971-6. PMID: 20855695; X-3, X-4


3065. Cavaleiro LHS, Viana FO, Unger DAA, et al. Propranolol for extensive hemangiomas of infancy: Two case reports


3075. Chow WC, Ha SY, Chan GCF. Vincristine can induce regression of vascular malformation in long standing refractory Kasabach Merritt phenomenon. Hong Kong Journal of Paediatrics. 2011;16(2):121-4. PMID: 2011235414; X-1


3271. Winland RD. Something is better than nothing. AGD Impact. 2011;39(6):4-. PMID: X-1


3408. Kupeli S, Cimen D, Kupeli BY. Successful treatment with propranolol in a patient with a segmental hemangioma: A case report


3445. Potts MB, Chang EF, Young WL, et al. Transsylvian-transinsular approaches to the insula and basal ganglia: operative techniques and results with vascular lesions. Neurosurgery. 2012 Apr;70(4):824-34; discussion 34. PMID: 21937930; X-1


3511. Xue K, Hildebrand GD. Topical timolol maleate 0.5% for infantile capillary haemangioma of the eyelid. Br J Ophthalmol. 2012 Dec;96(12):1536-7. PMID: 23014679; X-3, X-4


3676. Nanduri J. Epigenetic factors and the pathophysiological manifestation of sleep apnea. Somnologie. 2013 October;17:18. PMID: 71336340; X-1


Appendix D. Methods for Network Meta-Analysis

Using data extracted by the systematic review, we conducted a multi-intervention (network) meta-analysis to estimate the effectiveness of several corticosteroids and beta-blockers for the treatment of infantile hemangioma. Of particular interest was the estimation of the efficacy of propranolol, a beta-blocker that was used in a large number of studies in the review. To this end, we estimated the expected clearance of IH following intervention based on outcomes from 17 unique studies obtained from the systematic review. This set included outcomes for 4 different non-control pharmacologic interventions: propranolol, timolol, triamcinolone, and oral steroids.

A challenge for meta-analyzing these outcomes is the diversity in outcome reporting among the constituent studies. Though most used some measure of the reduction in the original IH at end of treatment, typically results were reported as counts of subjects achieving some arbitrary minimum clearance threshold, such as 50% or 75%. An approach to analyzing outcomes reported in this way is via a binomial model. For this model, the response variable is the number of individuals in study $j$ under intervention $k$ that achieve the clearance threshold:

$$y_{jk} = \sum_{i=1}^{n_{jk}} I_i(\text{above clearance threshold})$$

where $I$ is the indicator function, returning 1 if the argument is true, or 0 otherwise. This outcome can then modeled as a binomial response:

$$y_{jk} \sim Bin(n_{jk}, \pi_{jk})$$

where $\pi_{jk}$ is the probability of a positive response for study $j$ under intervention $k$. To allow for heterogeneity in this probability across studies, we can specify it as a random effect:

$$\text{logit}(\pi_{jk}) = \theta_{jk}$$

$$\theta_{jk} \sim \text{Normal}(\mu_k, \sigma_k)$$

where $\mu_k, \sigma_k$ are the parameters of a normal distribution (which, inverse logit-transformed, models quantities on the [0,1] interval).

However, the use of an arbitrary cutoff value as a threshold of success is an unsatisfactory modeling choice because there is an inherent loss of information in the dichotomization or discretization of continuous variables, and this loss is magnified here by having to discard data from studies that use a different response threshold than the adopted value (e.g. 75%). Since the clearance rate is a continuous measure, one can hypothesize a latent, continuous probability distribution that each study reports relative to specific quantiles: 50%, 75%, etc. If there is sufficient information, one may use a Bayesian approach to attempt to reconstruct this latent distribution, which would allow for more of the available information to be used in the meta-analytic procedure.

Under treatment $k$, one can consider a notional distribution of hemangioma clearance rates, from no effect (0) to complete clearance (1)—for our purposes, we will not consider IH enlargement, other than assigning it a “no effect” outcome. As a matter of convenience in a particular study $j$, researchers chose a clearance threshold $c_j$, only reporting whether a particular subject occupied one side or the other of this threshold. We can characterize the true, latent response distribution by estimating the parameters via the following identity:

$$\pi_{jk} = 1 - \Phi(c_j | \mu_k, \sigma_k)$$
where $\Phi(x)$ is the cumulative distribution function of the normal distribution (our latent distribution) under parameters evaluated at $x$. The resulting probability is the same as specified above, and can be used in the same binomial likelihood:

$$y_{jk} \sim Bin(n_{jk}, \pi_{jk})$$

This can be readily generalized to studies that report multiple thresholds, simply by dividing the distribution of $\pi_{jk}$ into regions corresponding to each threshold. This corresponds to a multinomial, rather than binomial, likelihood.

In principle, one may incorporate covariates to improve the prediction of intervention effectiveness. For example, the mode of delivery (oral, intralesional, topical), dose, or the hemangioma location may be predictive of intervention effectiveness. In this work, only propranolol had a sufficient number of studies to estimate covariate effects; we included an indicator variable for intralesional mode of delivery, relative to the oral mode that was used as a baseline. The logit-expected value of treatment $k$ from study $j$ was modeled as:

$$\theta_{jk} = \mu + \beta_k + \psi z_j + \epsilon_j$$

where $\mu$ is the baseline (control) clearance rate, $\beta_k$ is the relative effect of treatment $k$, $z_j$ is an indicator for the use of intralesional propranolol, and $\psi$ the associated relative intralesional effect. Finally, $\epsilon_j$ is a study random effect that is assigned to all treatment arms of study $j$, which accounts for the lack of independence within-study. This random effect was assumed to be normally distributed with zero mean and variance $\sigma^2$ that was estimated from the data.

A handful of studies, rather than reporting threshold counts, reported summary statistics of VAS scores for each study arm. Using the latent variable framework described above under a Bayesian estimation approach, this information can also be brought to bear on the estimation of the model parameters. This required the transformation of the reported outcomes from the VAS scale (0-100) to values on the real line (i.e. a logit transformation), including the reported standard deviation, which was transformed using the delta method. The resulting transformed values can then be used to inform the expected outcome for the corresponding intervention via a normal likelihood:

$$\text{logit}(\text{VAS}_{jk}) \sim N(\theta_{jk}, \sigma_j^2)$$

where $\sigma_j^2$ is the transformed standard deviation for the outcome.

Finally, one study (Qiu 2013) reported individual patient data in the form of VAS scores. This data was integrated into the study via the same method as for the summarized VAS score output outlined above, except that the delta transformation was not necessary, since the data were used directly.

This model was implemented in the PyMC package for Bayesian analysis in Python (Patil et al. 2010). Parameter estimates were obtained using Markov chain Monte Carlo (MCMC, Brooks et al. 2011) methods. Sampling was carried out for 100,000 iterations, with the first 90,000 conservatively discarded as burn-in to ensure convergence of the sampler. In order to evaluate convergence using the Gelman-Rubin diagnostic (Gelman and Rubin 1992), a second chain was sampled of identical size. The complete analysis is available in an open-access GitHub repository (https://github.com/fonnesbeck/IH_meta-analysis), including an IPython Notebook containing the model described above (https://github.com/fonnesbeck/IH_meta-analysis/blob/master/Infantile%20Hemangioma%20Meta-analysis.ipynb).
Model Results

The expected efficacy of control arms was estimated to be 0.06 (95% Bayesian credible interval = [0.01, 0.11]). All non-control treatments were estimated to have a larger expected clearance than control (Figure D-1). The largest mean estimate was oral propranolol (0.95, 95% BCI = [0.88, 0.99]), followed by timolol (0.62, 95% BCI = [0.39, 0.83]) and triamcinolone (0.58, 95% BCI = [0.22, 0.93]). Oral steroids had a mean clearance estimate of 0.43 (95% BCI = [0.21, 0.66]).

We calculated the probability that each of the non-control interventions is the best treatment, based on expected clearance rate. This was estimated from the MCMC simulation that tallied the number of iterations that each intervention had the highest expected value, and calculating the proportion for each intervention as an estimate of the probability of being best. Oral propranolol had the highest probability (99%), followed by triamcinolone (1%); all others had probabilities less than 1% combined. To better account for the uncertainty in the estimated treatment effects, we also calculated the surface under the cumulative ranking curve (SUCRA) for each treatment, which provides a probabilistic summary of the rankings of the treatments (Figure D-3). Oral propranolol had the highest SUCRA score (0.902), intralesional propanolol the lowest (0.119), with the other treatments intermediate.

Propanolol was estimated to have the largest variability in clearance rate (Figure D-2, σ=2.5, 95% BCI = [2.1, 2.9]) with timolol (σ=1.5, 95% BCI: 1.4 to 1.6), intralesional triamcinolone (σ=1.8, 95% BCI: 1.3 to 2.3), and oral steroids (σ=1.3, 95% BCI: 1.1 to 1.6) yielding similar, lower estimates. With the exception of Timolol, interventions with larger effect sizes tended to have larger effect size variance.

Table D-1. Posterior estimates of effect size

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<th>Mean</th>
<th>SE</th>
<th>95% Credible interval</th>
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<td>Oral propranolol</td>
<td>6.0</td>
<td>0.7</td>
<td>[4.6, 7.5]</td>
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<tr>
<td>Timolol</td>
<td>3.5</td>
<td>0.5</td>
<td>[2.4, 4.6]</td>
</tr>
<tr>
<td>Triamcinolone</td>
<td>3.3</td>
<td>0.8</td>
<td>[1.7, 4.9]</td>
</tr>
<tr>
<td>Oral steroid</td>
<td>2.6</td>
<td>0.5</td>
<td>[1.8, 3.6]</td>
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Note: 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.
Figure D-1. Estimates of expected IH clearance

Note: Estimates of expected IH clearance (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 D-2. Estimates of the variation of each treatment

Note: Estimates of the variation of each treatment, expressed as standard deviation, along with associated posterior interquartile range (thick lines) and 95% credible interval (thin lines).
To give an overview of the expected distribution of clearance rates across treatments, Figure D-4 plots estimated probability distribution functions based on the posterior clearance rates and standard deviations of four treatments. For each of 100 iterations, a sample was drawn from the posterior distributions of both the mean and standard deviation for oral propranolol, timolol, triamcinolone, and oral steroid. Inverse-logit transforming the normal probability distribution function resulted in plots that integrate the residual uncertainty of the parameters with the sampling variability of the model.
Figure D-4. 100 posterior samples of distribution of clearance rates under oral propranolol, timolol, triamcinolone, and oral steroid

The network diagram in Figure D-5 illustrates the relative numbers of direct comparisons between intervention types. The largest number (thickest line) is four comparisons.
Figure D-5. Network diagram of comparisons
References
Appendix E. Study Design Classification Algorithm

Figure E-1. Study design algorithm

Adapted by Jeff Andrews from Zaza et al. 2000, American Dietetic Association, and Cochrane
## Appendix F. Quality/Risk of Bias Ratings

### Table F-1. Quality assessment of randomized controlled trials

<p>| Author, Year                  | Allocation Sequence Generated Adequately | Allocation Treatment Adequately Concealed | Participants Analyzed in Groups Originally Assigned | Design Account for Confounding | Rule Out Impact from Concurrent Intervention or Unintended Exposure | Fidelity Maintained to Intervention Protocol | If Attrition, Were Missing Data Handled Appropriately | Difference in Length of Follow-up Between Groups | Outcome Assessors Blinded | Interventions/Exposures Assessed Clearly | Outcomes Assessed Clearly | Potential Outcomes Prespecified | All Prespecified Outcomes Reported | Risk of Bias Rating for Outcome |
|------------------------------|------------------------------------------|-------------------------------------------|-----------------------------------------------------|-------------------------------|-------------------------------------------------------------------|---------------------------------------------|--------------------------------------------------------|--------------------------------------------------|------------------------------------------|--------------------------------|-------------------------------|---------------------------------|-------------------------------|---------------------------------|----------------------------------|
| Leaute-Labreze 2015¹         | Yes                                      | Yes                                       | Yes                                                 | Yes                           | Yes                                                               | Yes                                         | No                                                     | Yes                                              | Yes                                      | Yes                                      | Yes                            | Yes                             | Yes                              | Good                             |
| Tawfik 2015²                 | Unclear                                  | Yes                                       | Yes                                                 | Yes                           | Yes                                                               | No                                          | No                                                     | Yes                                              | Yes                                      | Yes                                      | Yes                            | Yes                              | Yes                              | Fair                             |
| Abarzua-Araya 2014³          | Unclear                                  | Unclear                                  | Yes                                                 | No                            | No                                                                | Unclear                                   | Yes                                                    | No                                               | Yes                                      | Yes                                      | Yes                            | Yes                              | Yes                              | Fair                             |
| Bauman 2014⁴                | Yes                                      | Yes                                       | Yes                                                 | Yes                           | Yes                                                               | Unclear                                   | No                                                     | Yes                                              | Yes                                      | Yes                                      | Yes                            | Yes                              | Yes                              | Good                             |
| Chan 2013¹                   | Yes                                      | Yes                                       | Yes                                                 | Un unclear                   | Yes                                                               | Yes                                         | No                                                     | Yes                                              | Yes                                      | Yes                                      | Yes                            | Yes                              | Yes                              | Good                             |
| Kessels 2013⁶                | Yes                                      | Yes                                       | Yes                                                 | Yes                           | Yes                                                               | Yes                                         | No                                                     | Yes                                              | Yes                                      | No                                       | Yes                            | Yes                              | Yes                              | Good                             |
| Leaute-Labreze 2013⁷         | Yes                                      | Unclear                                  | Yes                                                 | No                            | Un unclear                                                       | Yes                                         | Yes                                                    | No                                               | Yes                                      | Yes                                      | Yes                            | Yes                              | Yes                              | Fair                             |
| Malik 2013⁸                  | Yes                                      | Un unclear                               | Yes                                                 | No                            | Yes                                                               | Unclear                                   | No                                                     | Yes                                              | Yes                                      | Yes                                      | Yes                            | Yes                              | Yes                              | Fair                             |
| Zaher 2013⁹                  | Unclear                                  | Unclear                                  | Yes                                                 | No                            | Yes                                                               | Unclear                                   | Unclear                                                | Yes                                              | Yes                                      | Yes                                      | Yes                            | Yes                              | Yes                              | Fair                             |</p>
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Table F-2. Quality assessment of cohort studies

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Table F-3. Quality assessment of studies reporting harms
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<td>Were the statistical methods used to assess the main harm or adverse event outcomes adequate?</td>
<td>Rating</td>
</tr>
<tr>
<td>--------------</td>
<td>---------------------------------------------------------------------</td>
<td>---------------------------------------</td>
<td>------------------------------------------------------------------------</td>
<td>---------------------------------------------------------------------------------</td>
<td>--------</td>
</tr>
<tr>
<td>Jalil 2006(^{13})</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Good</td>
</tr>
<tr>
<td>Kono 2006(^{14})</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Yes</td>
<td>Poor</td>
</tr>
<tr>
<td>Garzon 2005(^{129})</td>
<td>No</td>
<td>Unclear</td>
<td>No</td>
<td>No</td>
<td>Poor</td>
</tr>
<tr>
<td>McHeik 2005(^{130})</td>
<td>No</td>
<td>Unclear</td>
<td>No</td>
<td>Yes</td>
<td>Poor</td>
</tr>
<tr>
<td>Nicolai 2005(^{128})</td>
<td>No</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Yes</td>
<td>Poor</td>
</tr>
<tr>
<td>Waldschmidt 2005(^{131})</td>
<td>No</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Yes</td>
<td>Poor</td>
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<tr>
<td>Vlachakis 2004(^{19})</td>
<td>No</td>
<td>Unclear</td>
<td>Unclear</td>
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<td>Poor</td>
</tr>
<tr>
<td>David 2003(^{132})</td>
<td>No</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unclear</td>
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<tr>
<td>Vlachakis 2003(^{133})</td>
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<td>No</td>
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<td>Poor</td>
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<tr>
<td>Batta 2002(^{15})</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Good</td>
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<td>Akyuz 2001(^{46})</td>
<td>No</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Poor</td>
</tr>
<tr>
<td>Chang 2001(^{41})</td>
<td>No</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Poor</td>
</tr>
<tr>
<td>Demiri 2001(^{134})</td>
<td>No</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Yes</td>
<td>Poor</td>
</tr>
<tr>
<td>Hohenleutner 2001(^{135})</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unclear</td>
<td>No</td>
<td>Poor</td>
</tr>
<tr>
<td>Author, Year</td>
<td>Were the harms predefined using standardized or precise definitions?</td>
<td>Were all pre-specified harms reported?</td>
<td>Did the author(s) use STANDARD scale(s) or checklist(s) for harms collection?</td>
<td>Were the statistical methods used to assess the main harm or adverse event outcomes adequate?</td>
<td>Rating</td>
</tr>
<tr>
<td>---------------</td>
<td>---------------------------------------------------------------------</td>
<td>----------------------------------------</td>
<td>--------------------------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------------</td>
<td>--------</td>
</tr>
<tr>
<td>Raulin 2001</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Good</td>
</tr>
<tr>
<td>Chen 2000</td>
<td>No</td>
<td>Unclear</td>
<td>No</td>
<td>Yes</td>
<td>Poor</td>
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<tr>
<td>Poetke 2000</td>
<td>No</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Yes</td>
<td>Poor</td>
</tr>
<tr>
<td>Blei 1999</td>
<td>Partial</td>
<td>Unclear</td>
<td>Partial</td>
<td>Yes</td>
<td>Poor</td>
</tr>
<tr>
<td>Boon 1999</td>
<td>No</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Yes</td>
<td>Poor</td>
</tr>
<tr>
<td>Zide 1997</td>
<td>No</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Yes</td>
<td>Poor</td>
</tr>
<tr>
<td>Gangopadhyay</td>
<td>No</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Yes</td>
<td>Poor</td>
</tr>
<tr>
<td>Sadan 1996</td>
<td>No</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Yes</td>
<td>Poor</td>
</tr>
<tr>
<td>Chowdri 1994</td>
<td>No</td>
<td>Unclear</td>
<td>No</td>
<td>Yes</td>
<td>Poor</td>
</tr>
<tr>
<td>Morelli 1994</td>
<td>No</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Yes</td>
<td>Poor</td>
</tr>
<tr>
<td>Preeyanont 1994</td>
<td>No</td>
<td>Unclear</td>
<td>No</td>
<td>No</td>
<td>Poor</td>
</tr>
<tr>
<td>Morrell 1991</td>
<td>No</td>
<td>Unclear</td>
<td>No</td>
<td>Yes</td>
<td>Poor</td>
</tr>
<tr>
<td>Kushner 1990</td>
<td>No</td>
<td>Unclear</td>
<td>No</td>
<td>Yes</td>
<td>Poor</td>
</tr>
<tr>
<td>Achauer 1989</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Good</td>
</tr>
<tr>
<td>Author, Year</td>
<td>Were the harms predefined using standardized or precise definitions?</td>
<td>Were all pre-specified harms reported?</td>
<td>Did the author(s) use STANDARD scale(s) or checklist(s) for harms collection?</td>
<td>Were the statistical methods used to assess the main harm or adverse event outcomes adequate?</td>
<td>Rating</td>
</tr>
<tr>
<td>-----------------------</td>
<td>---------------------------------------------------------------------</td>
<td>----------------------------------------</td>
<td>--------------------------------------------------------------------------------</td>
<td>------------------------------------------------------------------------------------------</td>
<td>--------</td>
</tr>
<tr>
<td>Sloan 1989[148]</td>
<td>No</td>
<td>Unclear</td>
<td>No</td>
<td>Yes</td>
<td>Poor</td>
</tr>
<tr>
<td>Kushner 1985[149]</td>
<td>No</td>
<td>Unclear</td>
<td>No</td>
<td>No</td>
<td>Poor</td>
</tr>
<tr>
<td>Healy 1984[150]</td>
<td>No</td>
<td>Unclear</td>
<td>No</td>
<td>Yes</td>
<td>Poor</td>
</tr>
<tr>
<td>Sharma 1983[151]</td>
<td>No</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Yes</td>
<td>Poor</td>
</tr>
</tbody>
</table>

References


## Appendix G. Applicability Tables

### Table G-1. Applicability of studies assessing imaging modalities

<table>
<thead>
<tr>
<th>Domain</th>
<th>Description of applicability of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>Infants with hemangiomas (with mean ages of 30 days and 34 weeks). Fair distribution of male and female patients.</td>
</tr>
<tr>
<td>Intervention</td>
<td>Radiologic evaluation of hepatic hemangioma to determine which lesions required intervention and radiologic evaluation of lumbosacral cutaneous hemangiomas to evaluate which were associated with occult spinal dysraphism</td>
</tr>
<tr>
<td>Comparators</td>
<td>Comparators included ultrasound, magnetic resonance imaging, computed tomography and angiography. If different modalities were utilized on the same patient, it was sometimes not at the same time point making comparison between methods difficult.</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Studies assessed imaging and clinical findings and with need for intervention for hepatic hemangiomas and the second study reviewed incidence of occult spinal dysraphism found in patients with lumbosacral hemangioma</td>
</tr>
<tr>
<td>Setting</td>
<td>Studies were conducted in the US, Canada and Spain at tertiary care centers with referral programs for hemangiomas / vascular malformations</td>
</tr>
</tbody>
</table>

### Table G-2. Applicability of studies assessing steroids

<table>
<thead>
<tr>
<th>Domain</th>
<th>Description of applicability of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>Infants and children with IH (ages ranging from less than one to 72 months). Typically more females.</td>
</tr>
<tr>
<td>Intervention</td>
<td>Corticosteroids including topical, intralesional, intravenous, and oral forms.</td>
</tr>
<tr>
<td>Comparators</td>
<td>Comparators included another steroid or observation.</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Studies generally assessed change in lesion size and/or appearance and rebound growth. Two studies assessed vision outcomes. Comparative studies and case series also reported harms.</td>
</tr>
<tr>
<td>Setting</td>
<td>One comparative study was conducted in Canada and the others in the Netherlands, Germany, Turkey, Pakistan, and India. Applicability of some findings may be limited given differences in the systems of care in lower resource countries. Several comparative studies were also published between 2001 and 2010 and may not reflect current standards of care.</td>
</tr>
</tbody>
</table>

IH-infantile hemangioma

### Table G-3. Applicability of studies assessing beta-blockers

<table>
<thead>
<tr>
<th>Domain</th>
<th>Description of applicability of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>Studies typically included infants of both sexes ages 1 to 12 months of age (range: 1 month to 9 years of age) with infantile hemangiomas which included superficial, deep, and mixed lesions primarily involving the head and neck and occurring as focal or segmental lesions.</td>
</tr>
<tr>
<td>Intervention</td>
<td>Patients 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) for a variety of treatment durations most commonly up to 6 months duration.</td>
</tr>
<tr>
<td>Comparators</td>
<td>Comparators included other formulations of the same beta-blocker, other beta-blockers, untreated historical controls, treated historical controls, and non-beta-blocker comparators (topical imiquimod, oral and intralesional steroids, laser, and intralesional bleomycin).</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Studies commonly assessed final response based on size, volume, and/or coloration of IH, resolution of ulceration if present at initiation of therapy, and visual acuity or resolution of ptosis for periocular lesions. Assessments were obtained throughout therapy but final outcome assessments were typically performed following 24 weeks of treatment. Additional assessments for serious harms including bronchial hyperreactivity, hypoglycemia, bradycardia, and hypotension and less severe harms including sleep disturbances, cold extremities, and gastrointestinal complaints were monitored in the majority of studies.</td>
</tr>
<tr>
<td>Setting</td>
<td>Studies were conducted globally, often in specialty referral centers.</td>
</tr>
</tbody>
</table>
Table G-4. Applicability of studies assessing surgical and laser studies

<table>
<thead>
<tr>
<th>Domain</th>
<th>Description of applicability of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>Studies typically included infants of both sexes, with preponderance of females ages 1 week to 43 years of age with superficial and cutaneous infantile hemangiomas in varied locations.</td>
</tr>
<tr>
<td>Intervention</td>
<td>Patients were treated with a variety of lasers including pulse dyed, Nd:YAG, argon, cryotherapy, and intense pulsed light photothermolysis; in most cases, lasers were used as first-line treatment, which is not general, current clinical practice. Some studies used laser in combination with a beta-blocker like timolol or propranolol or combined laser modalities.</td>
</tr>
<tr>
<td>Comparators</td>
<td>Comparators included other lasers, different pulse lengths, different cooling regimens, and observation.</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Studies commonly assessed final response based on size, volume, and/or coloration of IH. Harms associated with laser treatment included skin atrophy, bleeding, scarring, ulceration and pigment changes.</td>
</tr>
<tr>
<td>Setting</td>
<td>Studies were conducted in the United States, United Kingdom, Netherlands, Germany, Greece, Japan and Singapore, typically in referral centers.</td>
</tr>
</tbody>
</table>

IH-infantile hemangioma
Appendix H. Harms Reported in Package Insert Data and Other Sources

Infantile Hemangioma Package Insert and FDA Harms Data

The harms data provided in this section were gathered from analyzing available gray literature (i.e., package inserts and FDA review packages). FDA approval packages were limited to those available on the FDA website that contained a “Medical Review” section of the document. Many of the review packages did not contain pediatric data and therefore the adult data was used. Table 1 includes the relevant indications for pediatric medications referenced in the clinical studies included in this review. Medications that have not been approved as safe and effective in pediatric patients and therefore are only FDA approved in adults are referenced in Table 2. Notable contraindications and warnings/precautions that would be relevant to consider in the pediatric population were included in the tables (drug interactions were not included). As a result, the data provided in this chart is not an all-inclusive list of these package insert sections. For complete data please see the corresponding package insert.

Table H-1: FDA Approved Pediatric Medications Included in Literature Review

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage Form</th>
<th>FDA Approved Indication</th>
<th>Contraindications</th>
<th>Warnings/ Precautions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemangeol ® (propranolol hydrochloride)¹</td>
<td>Oral solution</td>
<td>Beta-adrenergic blocker indicated for the treatment of proliferating infantile hemangioma requiring systemic therapy</td>
<td>• Premature infants with corrected age &lt;5 weeks • Infants weighing less than 2 kg • Asthma or history of bronchospasm • Bradycardia (&lt;80 beats per minute), greater than first degree heart block, decompensated heart failure • Blood pressure &lt;50/30 mmHg • Pheochromocytoma</td>
<td>• Hypoglycemia: Administer during or after feeding. Do not use in patients who are not able to feed or are vomiting. • Bradycardia and hypotension • Bronchospasm: Avoid use in patients with asthma or lower respiratory infection. • Increased risk of stroke in PHACE syndrome</td>
</tr>
<tr>
<td>Flo-pred® (prednisolone acetate)²</td>
<td>Oral suspension</td>
<td>• Allergic Conditions: Control of severe or incapacitating allergic conditions intractable to adequate trials of</td>
<td>---</td>
<td>• Hypothalamic-pituitary-adrenal (HPA) axis suppression, Cushing’s syndrome and hyperglycemia: Monitor patients for these conditions with chronic use. Taper doses gradually for withdrawal after chronic use.</td>
</tr>
</tbody>
</table>

H-1
| Orapred ODT (prednisolon sodium phosphate) | ODT tablet | conventional treatment in adults and pediatric populations with: | • Infections: Increased susceptibility to new infection and increased risk of exacerbation, dissemination, or reactivation of latent infection. Signs and symptoms of infection may be masked
• Elevated blood pressure, salt and water retention and hypokalemia: Monitor blood pressure and sodium, potassium serum levels
• GI perforation: increased risk in patients with certain GI disorders. Signs and symptoms may be masked
• Behavioral and mood disturbances: May include euphoria, insomnia, mood swings, personality changes, severe depression, and psychosis. Existing conditions may be aggravated.
• Decreases in bone density: Monitor bone density in patients receiving long-term corticosteroid therapy.
• Ophthalmic effects: May include cataracts, infections and glaucoma. Monitor intraocular pressure if corticosteroid therapy is continued for more than 6 weeks.
• Live or live attenuated vaccines: Do not administer to patients receiving immunosuppressive doses of corticosteroids.
• Negative effects on growth and development: Monitor pediatric patients on long-term corticosteroid therapy.
• Kaposi's sarcoma has been reported to occur in patients receiving corticosteroid therapy, most often for chronic conditions. Discontinuation of corticosteroids may result in clinical improvement.
• Although controlled clinical trials have shown corticosteroids to be effective in speeding the resolution of acute exacerbations of multiple sclerosis, they do not show that corticosteroids affect the ultimate outcome or natural history of the disease. The studies do show that relatively high doses of corticosteroids are necessary to demonstrate a significant effect.
• An acute myopathy has been observed with the use of high doses of corticosteroids, most often occurring in patients with disorders of neuromuscular transmission (e.g., myasthenia gravis), or in patients receiving concomitant therapy with neuromuscular blocking drugs (e.g., pancuronium). This acute myopathy is generalized, may involve ocular and respiratory muscles, and may result in quadriaparesis. Elevation of creatinine kinase may occur. Clinical improvement or recovery after stopping corticosteroids may require weeks to years.

| Rayos® (prednisone) | Delayed release tablet | • Dermatologic Diseases
  o Atopic dermatitis
  o Drug hypersensitivity reactions
  o Seasonal or perennial allergic rhinitis
  o Serum sickness
  • Endocrine Conditions
  o Congenital adrenal hyperplasia
  o Hypercalcemia of malignancy
  o Nonsuppurative thyroiditis
  o Primary or secondary adrenocortical insufficiency: hydrocortisone or cortisone is the first choice: synthetic analogs may be used in conjunction with mineralocorticoids where applicable
  • Gastrointestinal Diseases: During acute episodes in:
    o Crohn's Disease
    o Ulcerative colitis
  • Hematologic Diseases
  • Infections: Increased susceptibility to new infection and increased risk of exacerbation, dissemination, or reactivation of latent infection. Signs and symptoms of infection may be masked
  • Elevated blood pressure, salt and water retention and hypokalemia: Monitor blood pressure and sodium, potassium serum levels
  • GI perforation: increased risk in patients with certain GI disorders. Signs and symptoms may be masked
  • Behavioral and mood disturbances: May include euphoria, insomnia, mood swings, personality changes, severe depression, and psychosis. Existing conditions may be aggravated.
  • Decreases in bone density: Monitor bone density in patients receiving long-term corticosteroid therapy.
  • Ophthalmic effects: May include cataracts, infections and glaucoma. Monitor intraocular pressure if corticosteroid therapy is continued for more than 6 weeks.
  • Live or live attenuated vaccines: Do not administer to patients receiving immunosuppressive doses of corticosteroids.
  • Negative effects on growth and development: Monitor pediatric patients on long-term corticosteroid therapy.
  • Kaposi's sarcoma has been reported to occur in patients receiving corticosteroid therapy, most often for chronic conditions. Discontinuation of corticosteroids may result in clinical improvement.
  • Although controlled clinical trials have shown corticosteroids to be effective in speeding the resolution of acute exacerbations of multiple sclerosis, they do not show that corticosteroids affect the ultimate outcome or natural history of the disease. The studies do show that relatively high doses of corticosteroids are necessary to demonstrate a significant effect.
  • An acute myopathy has been observed with the use of high doses of corticosteroids, most often occurring in patients with disorders of neuromuscular transmission (e.g., myasthenia gravis), or in patients receiving concomitant therapy with neuromuscular blocking drugs (e.g., pancuronium). This acute myopathy is generalized, may involve ocular and respiratory muscles, and may result in quadriaparesis. Elevation of creatinine kinase may occur. Clinical improvement or recovery after stopping corticosteroids may require weeks to years.

| • Atopic dermatitis
• Drug hypersensitivity reactions
• Seasonal or perennial allergic rhinitis
• Serum sickness
| • Bullous dermatitis herpetiformis
• Contact dermatitis
• Exfoliative erythroderma
• Mycosis fungoides
• Pemphigus
• Severe erythema multiforme (Stevens-Johnson syndrome)
| • Congenital adrenal hyperplasia
• Hypercalcemia of malignancy
• Nonsuppurative thyroiditis
• Primary or secondary adrenocortical insufficiency: hydrocortisone or cortisone is the first choice: synthetic analogs may be used in conjunction with mineralocorticoids where applicable
| • Crohn's Disease
• Ulcerative colitis
| • Hematologic Diseases
| • Infections: Increased susceptibility to new infection and increased risk of exacerbation, dissemination, or reactivation of latent infection. Signs and symptoms of infection may be masked
• Elevated blood pressure, salt and water retention and hypokalemia: Monitor blood pressure and sodium, potassium serum levels
• GI perforation: increased risk in patients with certain GI disorders. Signs and symptoms may be masked
• Behavioral and mood disturbances: May include euphoria, insomnia, mood swings, personality changes, severe depression, and psychosis. Existing conditions may be aggravated.
• Decreases in bone density: Monitor bone density in patients receiving long-term corticosteroid therapy.
• Ophthalmic effects: May include cataracts, infections and glaucoma. Monitor intraocular pressure if corticosteroid therapy is continued for more than 6 weeks.
• Live or live attenuated vaccines: Do not administer to patients receiving immunosuppressive doses of corticosteroids.
• Negative effects on growth and development: Monitor pediatric patients on long-term corticosteroid therapy.
• Kaposi's sarcoma has been reported to occur in patients receiving corticosteroid therapy, most often for chronic conditions. Discontinuation of corticosteroids may result in clinical improvement.
• Although controlled clinical trials have shown corticosteroids to be effective in speeding the resolution of acute exacerbations of multiple sclerosis, they do not show that corticosteroids affect the ultimate outcome or natural history of the disease. The studies do show that relatively high doses of corticosteroids are necessary to demonstrate a significant effect.
• An acute myopathy has been observed with the use of high doses of corticosteroids, most often occurring in patients with disorders of neuromuscular transmission (e.g., myasthenia gravis), or in patients receiving concomitant therapy with neuromuscular blocking drugs (e.g., pancuronium). This acute myopathy is generalized, may involve ocular and respiratory muscles, and may result in quadriaparesis. Elevation of creatinine kinase may occur. Clinical improvement or recovery after stopping corticosteroids may require weeks to years.
<table>
<thead>
<tr>
<th>Neoplastic Conditions:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute leukemia</td>
</tr>
<tr>
<td>Aggressive lymphomas</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Nervous System Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute exacerbations of multiple sclerosis</td>
</tr>
<tr>
<td>Cerebral edema associated with primary or metastatic brain tumor, craniotomy or head injury</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ophthalmic Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sympathetic ophthalmia</td>
</tr>
<tr>
<td>Uveitis and ocular inflammatory conditions unresponsive to topical steroids</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Conditions Related to Organ Transplantation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute or chronic solid organ rejection</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pulmonary Diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allergic bronchopulmonary aspergillosis</td>
</tr>
<tr>
<td>Aspiration pneumonitis</td>
</tr>
<tr>
<td>Asthma</td>
</tr>
<tr>
<td>Fulminating or disseminated pulmonary tuberculosis when used concurrently with</td>
</tr>
</tbody>
</table>
appropriate chemotherapy
  o Hypersensitivity pneumonitis
  o Idiopathic bronchiolitis obliterans with organizing pneumonia
  o Idiopathic eosinophilic pneumonias
  o Idiopathic pulmonary fibrosis
  o Pneumocystis carinii pneumonia (PCP) associated with hypoxemia occurring in an HIV(+) individual who is also under treatment with appropriate anti-PCP antibiotics.
  o Symptomatic sarcoidosis

• Renal Conditions
  o To induce a diuresis or remission of proteinuria in nephrotic syndrome, without uremia, of the idiopathic type or that due to lupus erythematosus

• Rheumatologic Conditions: As adjunctive therapy for short-term administration (to tide the patient over an acute episode or exacerbation) in:
  o Acute gouty arthritis
  o During an exacerbation or as maintenance therapy in selected cases of:
|                     | o Ankylosing spondylitis  
|                     | o Dermatomyositis/poly  
|                     | myositis  
|                     | o Polymyalgia  
|                     | rheumatica  
|                     | o Psoriatic arthritis  
|                     | o Relapsing  
|                     | polychondritis  
|                     | o Rheumatoid arthritis,  
|                     | including juvenile  
|                     | rheumatoid arthritis  
|                     | (selected cases may  
|                     | require low dose  
|                     | maintenance therapy)  
|                     | o Systemic lupus  
|                     | erythematosus  
|                     | o Vasculitis  
| • Specific Infectious  
| Diseases | o Trichinosis with  
|         | neurologic or  
|         | myocardial  
|         | involvement.  
|         | o Tuberculous  
|         | meningitis with  
|         | subarachnoid block or  
|         | impending block used  
|         | concurrently with  
|         | appropriate  
|         | antituberculous  
|         | chemotherapy.  
|         | • Systemic fungal  
|         | infections  
|         | • Injectable  
|         | formulation: NOT  
|         | FOR USE IN  
|         | NEWBORNS  
| Similar Warnings/Precautions the prednisolone with the following  
| additional: | • In patients on corticosteroid therapy subjected to unusual stress,  
|         | increased dosage of rapidly acting corticosteroids before, during,  
|         | and after the stressful situation is indicated.  
|         | • The use of methylprednisolone tablets in active tuberculosis should  
|         | be restricted to those cases of fulminating or disseminated  
|         | tuberculosis in which the corticosteroid is used for the management  
|         | of the disease in conjunction with an appropriate antituberculous  
|         | regimen.

| Medrol® (methylprednisolone)³ | Oral tablet  
|                               | Intramuscular injection  
| Depo-Medrol® (methylprednisolone acetate)⁶ | • Similar Indications as  
|                                     | listed in the prednisolone  
|                                     | row with the following  
|                                     | additional:  
|                                     | o Acute and subacute  
|                                     | bursitis  
|                                     | o Synovitis of  
|                                     | osteoarthritis  
|                                     | o Acute nonspecific  
|                                     | tenosynovitis  

Similar Warnings/Precautions the prednisolone with the following  
additional:  
• In patients on corticosteroid therapy subjected to unusual stress,  
increased dosage of rapidly acting corticosteroids before, during,  
and after the stressful situation is indicated.  
• The use of methylprednisolone tablets in active tuberculosis should  
be restricted to those cases of fulminating or disseminated  
tuberculosis in which the corticosteroid is used for the management  
of the disease in conjunction with an appropriate antituberculous  
regimen.
| Solu-Medrol® (methylprednisolone sodium succinate) | Intravenous or intramuscular injection | • Post-traumatic osteoarthritis  
• Epicondylitis  
• Severe sebhorheic dermatitis  
• Severe psoriasis  
• Allergic corneal marginal ulcers  
• Herpes zoster ophthalmicus  
• Loeffler's syndrome not manageable by other means  
• Erythroblastopenia  
• Not indicated for:  
  - Crohn's Disease  
  - Transfusion reactions  
  - Pure red cell aplasia  
  - Vasculitis  
  - Allergic bronchopulmonary aspergillosis  
  - Aspiration pneumonitis  
  - Hypersensitivity pneumonitis  
  - Idiopathic bronchiolitis obliterans with organizing pneumonia  
  - Idiopathic pulmonary fibrosis  
  - Pneumocystis carinii pneumonia (PCP) associated with hypoxemia occurring in an HIV(+) individual who is also under treatment with appropriate anti-PCP antibiotics.  
  - Polymyalgia rheumatica  
  - Relapsing polychondritis | • If corticosteroids are indicated in patients with latent tuberculosis or tuberculin reactivity, close observation is necessary as reactivation of the disease may occur. During prolonged corticosteroid therapy, these patients should receive chemoprophylaxis.  
• Persons who are on drugs which suppress the immune system are more susceptible to infections than healthy individuals. Drug-induced secondary adrenocortical insufficiency may be minimized by gradual reduction of dosage. This type of relative insufficiency may persist for months after discontinuation of therapy; therefore, in any situation of stress occurring during that period, hormone therapy should be reinstituted. Since mineralocorticoid secretion may be impaired, salt and/or a mineralocorticoid should be administered concurrently.  
• There is an enhanced effect of corticosteroids on patients with hypothyroidism and in those with cirrhosis.  
• Corticosteroids should be used cautiously in patients with ocular herpes simplex because of possible corneal perforation.  
• The lowest possible dose of corticosteroid should be used to control the condition under treatment, and when reduction in dosage is possible, the reduction should be gradual.  
• Steroids should be used with caution in nonspecific ulcerative colitis, if there is a probability of impending perforation, abscess or other pyogenic infection; diverticulitis; fresh intestinal anastomoses; active or latent peptic ulcer; renal insufficiency; hypertension; osteoporosis; and myasthenia gravis.  
• Since complications of treatment with glucocorticoids are dependent on the size of the dose and the duration of treatment, a risk/benefit decision must be made in each individual case as to dose and duration of treatment and as to whether daily or intermittent therapy should be used.  

**Injection Specific:**  
• This product contains benzyl alcohol. Benzyl alcohol has been associated with a fatal “Gassing Syndrome” in premature infants and infants of low birth weight. Exposure to excessive amounts of benzyl alcohol has been associated with toxicity (hypotension, metabolic acidosis), particularly in neonates, and an increased incidence of kernicterus, particularly in small preterm infants. There have been rare reports of deaths, primarily in preterm infants, associated with exposure to excessive amounts of benzyl alcohol.  
• Rare instances of anaphylactoid reactions have occurred in patients receiving corticosteroid therapy |
Increased dosage of rapidly acting corticosteroids is indicated in patients on corticosteroid therapy subjected to any unusual stress before, during, and after the stressful situation.

Literature reports suggest an apparent association between use of corticosteroids and myocardial infarction; therefore, therapy with corticosteroids should be used with great caution in these patients.

Metabolic clearance of corticosteroids is decreased in hypothyroid patients and increased in hyperthyroid patients. Changes in thyroid status of the patient may necessitate adjustment in dosage.

Fungal Infections: Corticosteroids may exacerbate systemic fungal infections and therefore should not be used in the presence of such infections unless they are needed to control drug reactions. Corticosteroids should not be used in cerebral malaria.

Latent disease may be activated or there may be an exacerbation of intercurrent infections due to pathogens, including those caused by Amoeba, Candida, Cryptococcus, Mycobacterium, Nocardia, Pneumocystis, and Toxoplasma.

Tuberculosis: If corticosteroids are indicated in patients with latent tuberculosis or tuberculin reactivity, close observation is necessary as reactivation of the disease may occur. During prolonged corticosteroid therapy, these patients should receive chemoprophylaxis.

Viral Infections: Chicken pox and measles can have a more serious or even fatal course in pediatric and adult patients on corticosteroids.

Cardio-renal: As sodium retention with resultant edema and potassium loss may occur in patients receiving corticosteroids, these agents should be used with caution in patients with congestive heart failure, hypertension, or renal insufficiency.

Endocrine: Drug-induced secondary adrenocortical insufficiency may be minimized by gradual reduction of dosage. Although controlled clinical trials have shown corticosteroids to be effective in speeding the resolution of acute exacerbations of multiple sclerosis, they do not show that they affect the ultimate outcome or natural history of the disease.
An acute myopathy has been observed with the use of high doses of corticosteroids, most often occurring in patients with disorders of neuromuscular transmission (e.g., myasthenia gravis), or in patients receiving concomitant therapy with neuromuscular blocking drugs (e.g., pancuronium).

- Corticosteroids may suppress reactions to skin tests.
- Vaccines: Patients on prolonged corticosteroid therapy may exhibit a diminished response to toxoids and live or inactivated vaccines due to inhibition of antibody response. Corticosteroids may also potentiate the replication of some organisms contained in live attenuated vaccines. Routine administration of vaccines or toxoids should be deferred until corticosteroid therapy is discontinued if possible.

<table>
<thead>
<tr>
<th>Product</th>
<th>Indications</th>
<th>Warnings/Precautions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aristospan® (triamcinolone hexacetonide)</td>
<td>Alopecia areata, discoid lupus erythematosus, keloids, localized hypertrophic infiltrated, inflammatory lesions of granuloma annulare, lichen planus, lichen simplex chronicus (neurodermatitis), psoriatic plaques, necrobiosis lipoidica diabetorum, cystic tumors of an aponeurosis or tendon (ganglia)</td>
<td>Similar Warnings/Precautions to prednisolone with injection specific warnings in the methylprednisolone row.</td>
</tr>
<tr>
<td>Kenalog-10® (triamcinolone acetonide)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aristospan® (triamcinolone hexacetonide)</td>
<td>Alopecia areata, discoid lupus erythematosus, keloids, localized hypertrophic infiltrated, inflammatory lesions of granuloma annulare, lichen planus, lichen simplex chronicus (neurodermatitis), psoriatic plaques, necrobiosis lipoidica diabetorum, cystic tumors of an aponeurosis or tendon (ganglia)</td>
<td>Similar Warnings/Precautions to prednisolone with injection specific warnings in the methylprednisolone row.</td>
</tr>
<tr>
<td>Celestone Soluspan® (betamethasone)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NOT FOR USE IN NEWBORNS
| **Elocon®** (mometason furoate)\(^1\) | Topical cream | Corticosteroid indicated for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses in patients 2 years of age or older | --- | - Reversible HPA axis suppression with the potential for glucocorticosteroid insufficiency after withdrawal of treatment, Cushing's syndrome, and hyperglycemia may occur due to systemic absorption. Patients applying a topical steroid to a large surface area or to areas under occlusion should be evaluated periodically for evidence of HPA axis suppression. Modify use should HPA axis suppression develop.  
- Pediatric patients may be more susceptible to systemic toxicity.  
- Allergic Contact Dermatitis: If irritation develops, mometasone furoate should be discontinued and appropriate therapy instituted.  
- Concomitant Skin Infections: If concomitant skin infections are present or develop, an appropriate antifungal or antibacterial agent should be used. If a favorable response does not occur promptly, mometasone furoate use of should be discontinued until the infection has been adequately controlled. |
| **Zyclara®** (imiquimod)\(^2\) | 2.5% to 3.75% Topical cream | Indicated for the treatment of external genital and perianal warts (EGW)/condyloma acuminata in patients 12 years or older. | --- | - Local Skin Reactions: Intense local skin reactions including skin weeping or erosion can occur after a few applications and may require an interruption of dosing. Imiquimod has the potential to exacerbate inflammatory conditions of the skin, including chronic graft versus host disease. Severe local inflammatory reactions of the female external genitalia can lead to severe vulvar swelling. Severe vulvar swelling can lead to urinary retention. Dosing should be interrupted or discontinued for severe vulvar swelling. Administration of imiquimod is not recommended until the skin is healed from any previous drug or surgical treatment.  
- Systemic Reactions Flu-like signs and symptoms may accompany, or even precede, local skin reactions and may include fatigue, nausea, fever, myalgias, arthralgias, malaise and chills.  
- Ultraviolet Light Exposure Risks: Exposure to sunlight (including sunlamps) should be avoided or minimized during use of imiquimod.  
- Increased Risk of Adverse Reactions with Concomitant Imiquimod Use  
- Immune Cell Activation in Autoimmune Disease: Imiquimod should be used with caution in patients with pre-existing autoimmune conditions because imiquimod activates immune cells |
<p>| <strong>Aldara®</strong> (imiquimod)(^3) | 5% Topical cream | --- | --- | --- |</p>
<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage Form</th>
<th>FDA Approved Indication</th>
<th>Contraindications</th>
<th>Warnings/ Precautions</th>
</tr>
</thead>
</table>
| Tenormin® (atenolol) | Oral tablet | - Treatment of hypertension, to lower blood pressure  
- Long-term management of patients with angina pectoris.  
- Management of hemodynamically stable patients with definite or suspected acute myocardial infarction to reduce cardiovascular mortality | - Sinus bradycardia  
- Heart block greater than first degree  
- Cardiogenic shock  
- Overt cardiac failure | - Cardiac Failure: Sympathetic stimulation is necessary in supporting circulatory function in congestive heart failure, and beta blockade carries the potential hazard of further depressing myocardial contractility and precipitating more severe failure.  
- In Patients Without a History of Cardiac Failure: Continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure  
- Cessation of Therapy with Atenolol: Patients with coronary artery disease, who are being treated with atenolol, should be advised against abrupt discontinuation of therapy.  
- Concomitant Use of Calcium Channel Blockers: Bradycardia and heart block can occur and the left ventricular end diastolic pressure can rise when beta-blockers are administered with verapamil or diltiazem. Patients with pre-existing conduction abnormalities or left ventricular dysfunction are particularly susceptible.  
- Bronchospastic Diseases: Patients with bronchospastic disease should, in general, not receive beta blockers. Because of its relative beta1 selectivity, however, atenolol may be used with caution in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment.  
- Major Surgery: Chronically administered beta-blocking therapy should not be routinely withdrawn prior to major surgery, however the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.  
- Diabetes and Hypoglycemia: atenolol should be used with caution in diabetic patients if a beta-blocking agent is required. Beta blockers may mask tachycardia occurring with hypoglycemia, but other manifestations such as dizziness and sweating may not be significantly affected.  
- Thyrotoxicosis: Beta-adrenergic blockade may mask certain clinical signs (eg, tachycardia) of hyperthyroidism. Abrupt withdrawal of beta blockade might precipitate a thyroid storm; therefore, patients suspected of developing thyrotoxicosis from whom atenolol therapy is to be withdrawn should be monitored closely.  
- Untreated Pheochromocytoma: atenolol should not be given to patients with untreated pheochromocytoma. |
<table>
<thead>
<tr>
<th>Ophthalmic Solution</th>
<th>Treatment of elevated intraocular pressure in patients with ocular hypertension or open-angle glaucoma.</th>
</tr>
</thead>
</table>
| Timoptic® (timolol maleate) | - Bronchial asthma  
- A history of bronchial asthma  
- Severe chronic obstructive pulmonary disease  
- Sinus bradycardia  
- Second or third degree atroventricular block  
- Overt cardiac failure  
- Cardiogenic shock |
| Timoptic-XE® (timolol maleate) | - Cardiac Failure: sympathetic stimulation may be essential for support of the circulation in individuals with diminished myocardial contractility, and its inhibition of beta-adrenergic receptor blockade may precipitate more severe failure.  
- In Patients Without a History of Cardiac Failure: continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of cardiac failure, timolol should be discontinued.  
- Major Surgery: Beta-adrenergic receptor blockade impairs the ability of the heart to respond to beta-adrenergically mediated reflex stimuli. This may augment the risk of general anesthesia in surgical procedures. In patients undergoing elective surgery, some authorities recommend gradual withdrawal of beta-adrenergic receptor blocking agents.  
- Diabetes Mellitus: Beta-adrenergic blocking agents should be administered with caution in patients subject to spontaneous hypoglycemia or to diabetic patients (especially those with labile diabetes) who are receiving insulin or oral hypoglycemic agents. Beta-adrenergic receptor blocking agents may mask the signs and symptoms of acute hypoglycemia.  
- Thyrotoxicosis: Beta-adrenergic blocking agents may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism.  
- Because of potential effects of beta-adrenergic blocking agents on blood pressure and pulse, these agents should be used with caution in patients with cerebrovascular insufficiency  
- There have been reports of bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products.  
- Choroidal detachment after filtration procedures has been reported with the administration of aqueous suppressant therapy (e.g., timolol).  
- Angle-closure glaucoma: In patients with angle-closure glaucoma, the immediate objective of treatment is to reopen the angle. This requires constricting the pupil. Timolol maleate has little or no effect on the pupil. Timolol should not be used alone in the treatment of angle-closure glaucoma.  
- Anaphylaxis: While taking beta-blockers, patients with a history of atopy or a history of severe anaphylactic reactions to a variety of allergens may be more reactive to repeated accidental, diagnostic, or therapeutic challenge with such allergens.  
- Muscle Weakness: Beta-adrenergic blockade has been reported to potentiate muscle weakness consistent with certain myasthenic symptoms (e.g., diplopia, ptosis, and generalized weakness). |
| Betimol® (timolol) | - Cardiac Failure: sympathetic stimulation may be essential for support of the circulation in individuals with diminished myocardial contractility, and its inhibition of beta-adrenergic receptor blockade may precipitate more severe failure.  
- In Patients Without a History of Cardiac Failure: continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of cardiac failure, timolol should be discontinued.  
- Major Surgery: Beta-adrenergic receptor blockade impairs the ability of the heart to respond to beta-adrenergically mediated reflex stimuli. This may augment the risk of general anesthesia in surgical procedures. In patients undergoing elective surgery, some authorities recommend gradual withdrawal of beta-adrenergic receptor blocking agents.  
- Diabetes Mellitus: Beta-adrenergic blocking agents should be administered with caution in patients subject to spontaneous hypoglycemia or to diabetic patients (especially those with labile diabetes) who are receiving insulin or oral hypoglycemic agents. Beta-adrenergic receptor blocking agents may mask the signs and symptoms of acute hypoglycemia.  
- Thyrotoxicosis: Beta-adrenergic blocking agents may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism.  
- Because of potential effects of beta-adrenergic blocking agents on blood pressure and pulse, these agents should be used with caution in patients with cerebrovascular insufficiency  
- There have been reports of bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products.  
- Choroidal detachment after filtration procedures has been reported with the administration of aqueous suppressant therapy (e.g., timolol).  
- Angle-closure glaucoma: In patients with angle-closure glaucoma, the immediate objective of treatment is to reopen the angle. This requires constricting the pupil. Timolol maleate has little or no effect on the pupil. Timolol should not be used alone in the treatment of angle-closure glaucoma.  
- Anaphylaxis: While taking beta-blockers, patients with a history of atopy or a history of severe anaphylactic reactions to a variety of allergens may be more reactive to repeated accidental, diagnostic, or therapeutic challenge with such allergens.  
- Muscle Weakness: Beta-adrenergic blockade has been reported to potentiate muscle weakness consistent with certain myasthenic symptoms (e.g., diplopia, ptosis, and generalized weakness). |
Timolol has been reported rarely to increase muscle weakness in some patients with myasthenia gravis or myasthenic symptoms.
Harms Data for Medications Included in the Analysis

The following sections provide an overview of the common and notable adverse events of each medication. When possible, adverse event data specific for pediatric patients have been included. It is important to note that the information provided in this section is not an all-inclusive list of adverse events. Consult the corresponding package insert for complete information. Many of the adverse events reported are from various clinical trials used in support of the medication’s FDA approval. As a result, these trials many have been conducted under varying conditions and the adverse event rates may not reflect what is observed in clinical practice. In addition, these rates may not necessarily be able to be compared to the rates observed in the clinical trials of different drugs. Post-marketing adverse events are reported on a voluntary basis and therefore do not represent complete patient data.

Hemangeol® (propranolol hydrochloride)

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.¹ 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.¹ 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.

Additional Formulations

The safety and efficacy of the oral tablet, oral capsule, and injectable formulations of propranolol have not been investigated in pediatric patients.¹⁸⁻²⁰ The package inserts for these formulations state that reports of bronchospasm and congestive heart failure have been reported in pediatric patients receiving propranolol.

Post-marketing Adverse Events

Additional adverse events revealed during post-marketing surveillance include: agranulocytosis, hallucination and purpura.¹
Corticosteroids

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). 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. 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, insomnna, 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.

Flo-pred® (prednisolone acetate), Orapred ODT (prednisolone sodium phosphate)

The adverse events reported for Flo-pred® and Orapred ODT® in adult patients has been compiled from the package insert and the original FDA approval package assessing the safety of adult patients with rheumatoid arthritis. Common adverse events for Flo-pred and Orapred ODT have been reported in the common adverse events for corticosteroids in general (see above). Bioequivalence studies conducted in healthy volunteers assessing prednisolone oral suspension, prednisolone syrup, and prednisolone tablet were reported in the Flo-pred® original FDA approval document. The following adverse events were reported across 3 of these studies (see table 3).
<table>
<thead>
<tr>
<th>Study #</th>
<th>1</th>
<th>1</th>
<th>1</th>
<th>2</th>
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</thead>
<tbody>
<tr>
<td>Dosage form</td>
<td>Suspension (n=24)</td>
<td>Syrup (n=24)</td>
<td>Tablet (n=24)</td>
<td>Suspension (n=24)</td>
<td>Syrup (n=23)</td>
<td>Tablet (n=24)</td>
<td>Suspension (n=24)</td>
<td>Syrup (n=23)</td>
<td>Tablet (n=23)</td>
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<tr>
<td>Arthralgia</td>
<td>0</td>
<td>0</td>
<td>1 (4%)</td>
<td>0</td>
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<td>1 (4%)</td>
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</tr>
<tr>
<td>Headache</td>
<td>1 (4%)</td>
<td>0</td>
<td>0</td>
<td>3 (13%)</td>
<td>1 (4%)</td>
<td>6 (25%)</td>
<td>1 (4%)</td>
<td>1 (4%)</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>Somnolence</td>
<td>0</td>
<td>1 (4%)</td>
<td>0</td>
<td>1 (4%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>1 (4%)</td>
<td>1 (4%)</td>
<td>1 (4%)</td>
<td>1 (4%)</td>
<td>0</td>
<td>---</td>
<td>---</td>
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<tr>
<td>Fatigue</td>
<td>1 (4%)</td>
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<td>0</td>
<td>1 (4%)</td>
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<td>1 (4%)</td>
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<tr>
<td>Hot puncture Flash</td>
<td>0</td>
<td>1 (4%)</td>
<td>0</td>
<td>1 (4%)</td>
<td>1 (4%)</td>
<td>0</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Venipuncture site pain</td>
<td>1 (4%)</td>
<td>0</td>
<td>1 (4%)</td>
<td>0</td>
<td>1 (4%)</td>
<td>0</td>
<td>---</td>
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</tr>
<tr>
<td>Lymphocyte count increased</td>
<td>2 (8%)</td>
<td>2 (8%)</td>
<td>2 (8%)</td>
<td>1 (4%)</td>
<td>1 (4%)</td>
<td>1 (4%)</td>
<td>---</td>
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</tr>
<tr>
<td>Neutrophil count decreased</td>
<td>1 (4%)</td>
<td>1 (4%)</td>
<td>1 (4%)</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>2 (8%)</td>
<td>2 (9%)</td>
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<tr>
<td>Ocular hyperaemia</td>
<td>---</td>
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<td>---</td>
<td>1 (4%)</td>
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</tr>
<tr>
<td>Lip dry</td>
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<td>---</td>
<td>1 (4%)</td>
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<td>1 (4%)</td>
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<tr>
<td>Nausea</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>2 (8%)</td>
<td>1 (4%)</td>
<td>1 (4%)</td>
<td>1 (4%)</td>
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<td>0</td>
</tr>
<tr>
<td>Dizziness</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>1 (4%)</td>
<td>1 (4%)</td>
<td>1 (4%)</td>
<td>0</td>
<td>0</td>
<td>1 (4%)</td>
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<tr>
<td>Venipuncture site swelling</td>
<td>1 (4%)</td>
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<td>0</td>
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<td>---</td>
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<tr>
<td>Blood Bilirubin increase</td>
<td>1 (4%)</td>
<td>1 (4%)</td>
<td>1 (4%)</td>
<td>---</td>
<td>---</td>
<td>---</td>
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</tr>
<tr>
<td>Increased appetite</td>
<td>0</td>
<td>0</td>
<td>1 (4%)</td>
<td>---</td>
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<tr>
<td>Pharyngolaryngeal Pain</td>
<td>0</td>
<td>0</td>
<td>1 (4%)</td>
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<td>---</td>
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</tr>
<tr>
<td>Blister</td>
<td>1 (4%)</td>
<td>0</td>
<td>0</td>
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</tr>
<tr>
<td>Abdominal distension</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>0</td>
<td>0</td>
<td>1 (4%)</td>
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<tr>
<td>Abdominal pain</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>0</td>
<td>0</td>
<td>1 (4%)</td>
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<tr>
<td>Upper abdominal pain</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>0</td>
<td>0</td>
<td>1 (4%)</td>
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</tr>
<tr>
<td>Diarrhea</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>0</td>
<td>0</td>
<td>1 (4%)</td>
<td>---</td>
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</tr>
<tr>
<td>Dry mouth</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>1 (4%)</td>
<td>0</td>
<td>0</td>
<td>---</td>
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</tr>
<tr>
<td>Flatulence</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>1 (4%)</td>
<td>0</td>
<td>0</td>
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</tr>
<tr>
<td>Vomiting</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>1 (4%)</td>
<td>0</td>
<td>1 (4%)</td>
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<td>---</td>
</tr>
<tr>
<td>Vessel puncture site bruise</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>1 (4%)</td>
<td>0</td>
<td>0</td>
<td>---</td>
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</tr>
<tr>
<td>Tremor</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>1 (4%)</td>
<td>0</td>
<td>0</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Metrorrhagia</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>1 (4%)</td>
<td>0</td>
<td>0</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Nasal congestion</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>0</td>
<td>0</td>
<td>1 (4%)</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Rhinorrhea</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>0</td>
<td>0</td>
<td>1 (4%)</td>
<td>---</td>
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</tr>
</tbody>
</table>
Bioavailability studies were also conducted for Orapred ODT® in 24 health patients each receiving Orapred ODT® 30mg tablet, Pediapred® oral solution 30mg and Orapred® oral solution 30mg. Adverse events reported in patients taking Orapred ODT® included: face edema/swelling face, pharyngolaryngeal pain, blood in stool, eye irritation, and eyelid edema.

A search of the literature for adverse events associated with prednisolone was conducted by Taro Pharmaceuticals and reported in the FDA review package.21 The most common adverse events reported in 4 pediatric studies (mean age <2 years) using prednisolone 1-2 mg/kg/day (n=187) for less than 1 week included: vomiting-nausea (5%), diarrhea (3%), restlessness (2%), rash-exanthema (1%), and jittery (1%). The most common adverse events reported in 6 adult studies (mean age 40-60 years) using prednisolone 5-60 mg/day (n=189) for 2 weeks to 2 years included: vomiting-nausea (5%), rash-exanthema (5%), headache (9%), gastric distress (8%), insomnia (6%), weight gain (6%), abdominal pain (5%), mood swings (4%), aggravated RA (3%), and hypertension (3%).

### Post-marketing Adverse Events

Data specifically from pediatric patients reported in the Orapred ODT® original FDA approval documents included: urticaria (6), dyspea (1), wheezing (2), coughing (1), congestion (1), lethargy (1), confusion (1), could not stand or hold up head (1), back pain (1), double vision (1), slurred words (1), dizziness (1), difficulty breathing (1), tremor (1), dysphemia (1), head banging (1), and leukocytosis(1).22 Serious adverse events included: depression, headache, abdominal pain and malaise which occurred in 1 patient. Four patients experienced hypersensitivity reactions: rash, swelling, itching, redness in the mouth, pain, and difficulty swallowing. Other events reported included: hyperchlesterolemia and lack of response, audea, emesis, diarrhea and bluding fontanelle, increased heart rate, psychiatric events, erythema, pruritis and rash.

### Rayos® (prednisone)

The adverse events reported for Rayos® in adult patients has been compiled from the package insert and the original FDA approval package assessing the safety of adult patients with rheumatoid arthritis.4,23

Adverse events reported for Rayos® were similar to the common adverse events for corticosteroids in general (see above)4 An additional common adverse event specifically listed in the Rayos® package insert was central serous chorioretinopathy.

The medical review document for Rayos® reported adverse events occurring in >2% of patients participating in phase 3 clinical studies.23 These patients were treated with prednisone extended release (XL) (n=375) and prednisone immediate release tablets (IR) (n=144). Adverse events included: abdominal pain upper: XL=6 (<2%), IR=8 (6%); diarrhea: XL=4 (1%), IR=4 (3%); nausea: XL=8 (2%), IR=4 (3%); dyspepsia: XL=0, IR=3 (2%); nasopharyngitis: XL=16 (4%), IR=8 (6%); bronchitis: XL=5 (1%), IR=5 (4%); upper respiratory tract infection: XL=2
(<1%), IR=3 (2%); rheumatoid arthritis: XL=48 (13%), IR=14 (10%); vertigo: XL=4 (1%), IR=5 (4%); Headache: XL=15 (4%), IR=5 (4%); and chest pain: XL=2 (<1%), IR=0. In addition, hematology reference range changes have been reported in phase 3 clinical studies (see table 4).

<table>
<thead>
<tr>
<th>Table H-4: Hematology Changes23</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prednisone XL (n=375)</td>
</tr>
<tr>
<td>-------------------------</td>
</tr>
<tr>
<td>Hemoglobin (g/L)</td>
</tr>
<tr>
<td>Shift from Normal to Low</td>
</tr>
<tr>
<td>Shift from Normal to High</td>
</tr>
<tr>
<td>Shift from High to Low</td>
</tr>
<tr>
<td>WBC (x10^9/mcl)</td>
</tr>
<tr>
<td>Shift from Normal to Low</td>
</tr>
<tr>
<td>Shift from Normal to High</td>
</tr>
<tr>
<td>Basophils (%)</td>
</tr>
<tr>
<td>Shift from Normal to High</td>
</tr>
<tr>
<td>Eosinophils (%)</td>
</tr>
<tr>
<td>Shift from Normal to High</td>
</tr>
<tr>
<td>Lymphocytes (%)</td>
</tr>
<tr>
<td>Shift from Normal to Low</td>
</tr>
<tr>
<td>Shift from Normal to High</td>
</tr>
<tr>
<td>Monocytes (%)</td>
</tr>
<tr>
<td>Shift from Normal to Low</td>
</tr>
<tr>
<td>Shift from Normal to High</td>
</tr>
<tr>
<td>Shift from High to Low</td>
</tr>
<tr>
<td>Neutrophils (%)</td>
</tr>
<tr>
<td>Shift from Normal to Low</td>
</tr>
<tr>
<td>Shift from Normal to High</td>
</tr>
<tr>
<td>Platelets (x10^9/mcl)</td>
</tr>
<tr>
<td>Shift from Normal to Low</td>
</tr>
<tr>
<td>Shift from Normal to High</td>
</tr>
</tbody>
</table>

Chemistry reference range shifts from normal at baseline to high after treatment with prednisone extended release (XL) (n=375) and prednisone immediate release (IR) (n=144) in phase 3 studies included: alk phos (U/L): XL=6 (2%), IR=2 (1%); ALT/SGPT (U/L): XL=13 (4%), IR=5 (4%); AST/SGOT (U/L): XL=13 (4%), IR=7 (5%); GGT (U/L): XL=15 (4%), IR=8 (5%); bilirubin (umg/dL): XL=2 (<1%), IR=0; albumin (g/L): XL=2 (<1%), IR=0 (0%); protein (g/L): XL=3 (1%), IR=1 (<1%); cholestrol (mmol/L): XL=54 (14%), IR=15 (10%); triglycerides (mmol/L): XL=17 (5%), IR=15 (10%); BUN (mmol/L): XL=7 (2%), IR=0; creatinine (umol/L): XL=9 (2%), IR=3 (2%); glucose (mmol/L): XL=28 (8%), IR=18 (13%); calcium (mmol/L): XL=1 (<1%), IR=0; chloride (mmol/L): XL=3 (1%), IR=2 (1%); potassium (mmol/L): XL=6 (2%), IR=1 (<1%); and sodium (mmol/L): XL=8 (2%), IR=1 (<1%).23

**Serious Adverse Events**

Serious adverse events from controlled phase 3 studies reported in the FDA review document for extended release prednisone (XL) (n=375) and immediate release prednisone (IR) (n=144) include: myocardial infarction: XL=1 (<1%), IR=0; abdominal pain: XL=0, IR=1 (<1%); chest pain: XL=1 (<1%), IR=1 (<1%); sudden death: XL=0, IR=1 (<1%); tendon rupture: XL=0, IR=1 (<1%); osteoarthritis: XL=1 (<1%), IR=0; synovial cyst: XL=1 (<1%), IR = 0; squamous cell carcinoma: XL=1 (<1%), IR=0; depressed level of consciousness: XL=0, IR=1 (<1%); pulmonary embolism: XL=0, IR=1 (<1%); hospitalization: XL=1 (<1%), IR=0; and limb operation: XL=1 (<1%), IR=0.23
An additional clinical trial assessing the safety of prednisone extended release was conducted in Germany and included 2676 patients in the safety analysis. Serious adverse events reported included: gastrointestinal disorders (5 events, <1%), general disorders and administration site conditions (4 events; <1%), injury, poisoning and procedural complications (3 events; <1%) and skin and subcutaneous disorders (3 events; <1%), GI bleeding (1 event), hemorrhagic proctitis (1 event), stomach pain/ache (1 event), and red skin (1 event).

Discontinuations

The following adverse events led to discontinuation in patients taking extended release prednisone (XL) (n=375) and immediate release prednisone (IR) (n=144) in phase 3 clinical trials: palpitations: XL=1 (<1%), IR=0; vertigo: XL=0, IR=1 (1%); glaucoma: XL=1 (<1%), IR=0; abdominal pain: XL=1 (<1%), IR=0; upper abdominal pain: XL=0, IR=2 (1%); constipation: XL=1 (<1%), IR=0; dyspepsia: XL=1 (<1%), IR=0; gastroesophageal reflux disease: XL=0, IR=1 (1%); intestinal functional disorder: XL=0, IR=1 (1%); nausea: XL=0, IR=2 (1%); vomiting: XL=1 (<1%), IR=0; sudden death: XL=0, IR=1 (1%); rheumatoid arthritis: XL=5 (1%), IR=2 (1%); aphasia: XL=0, IR=1 (1%); depressed level of consciousness: XL=0, IR=1 (1%); dizziness: XL=0, IR=1 (1%); headache: XL=2 (1%), IR=1 (1%); anxiety: XL=1 (<1%), IR=0; insomnia: XL=2 (1%), IR = 0; sleep disorder: XL=1 (<1%), IR=0; renal pain: XL=0, IR=1 (1%); and secondary hypertension: XL=1 (<1%), IR=0.

Reasons for discontinuation in the German clinical trial (n=2676) assessing prednisone extended release included: nausea (22; 1%), upper abdominal pain (18; 1%), sleep disorders (16; 1%), RA (11; <1%), headache (9; <1%), dizziness (6; <1%) and glucose metabolism (3 patients with diabetes; <1%, and 3 patients with blood glucose increased; <1%).

Post-marketing Adverse Events

Horizon Pharma completed a search of the FDA’s Spontaneous Reporting system and the Adverse Event Reporting System for prednisone (date range: January 1, 1969 through March 31, 2010) and identified a total of 965,454 adverse events. Adverse events reported at a frequency of ≥0.5% included: diarrhea: 5293 (0.5%), nausea: 8419 (0.9%), vomiting: 4889 (0.5%), asthenia: 5541 (0.6%), condition aggravated: 5774 (0.6%), drug ineffective: 6078 (0.6%), fatigue: 5877 (0.6%), pyrexia: 11692 (1.2%), pneumonia: 6305 (0.7%), arthralgia: 5240 (0.5%), and dyspnea: 7570 (0.8%).

Medrol® (methylprednisolone), Depo-Medrol® (methylprednisolone acetate), Solu-Medrol® (methylprednisolone sodium succinate)

Adverse event data for Medrol®, Depo-Medrol®, and Solu-Medrol® was gathered from the corresponding package inserts. FDA approval packages were not available for any of the methylprednisolone products.

The use of Medrol® for pediatric patients was not included in the package inert. The adverse events for Medrol® included all of the adverse events listed in general for corticosteroids (see above) with the addition of: negative nitrogen balance due to protein catabolism. The following adverse events have been reported for general corticosteroids but were NOT included as adverse events for Medrol®: alteration in glucose tolerance, not behavioral and mood changes, mood swings, increased appetite and weight gain, bradycardia, cardiac arrest, cardiac arrhythmias, cardiac enlargement, circulatory collapse, fat embolism, abnormal fat deposits, hypertrophic cardiomyopathy in premature infants, myocardial rupture following recent myocardial infarction, pulmonary edema, syncope, tachycardia,
thromboembolism, thrombophlebitis, vasculitis, acne, cutaneous and subcutaneous atrophy, dry scalp, edema, hyper or hypopigmentation, sterile abscess, striae, thinning scalp hair, hirsutism, moon faces, hepatomegaly, hiccups, malaise, nausea, charcot-like arthropathy, arachnoiditis, depression, emotional instability, euphoria, insomnia, meningitis, neuritis, neuropathy, paraparesis/paraplegia, paresthesia, personality changes, sensory disturbances, and alteration in motility/number of spermatozoa.

Warnings for the use of Depo-Medrol® and Solu-Medrol® in pediatric patients due to the presence of benzyl alcohol have been described above (see table 1).6,7

Adverse events for Depo-Medrol® and Solu-Medrol® were similar to those listed in general for corticosteroids (see above) with the addition of: dry scaly skin, glycosuria, hypertrichosis, negative nitrogen balance due to protein catabolism, injection site infections following non-sterile administration, postinjection flare (following intra-articular use), temporary/permanent visual impairment including blindness associated with periocular injections and decreased resistance to infection.6,7

Depo-Medrol® has unique adverse events reported in addition to those listed above: calcinosis (following intra-articular or intra-lesional use), seizures, ocular and periocular inflammation including allergic reactions, and residue or slough at injection site.6

Additional adverse events reported for Solu-Medrol® included: rhinitis and burning or tingling (especially in the perineal area after intravenous injection).7

**Aristospan® (triamcinolone hexacetonide), Kenalog-10® (triamcinolone acetonide)**

Aristospan® (triamcinolone hexacetonide), Kenalog-10® (triamcinolone acetonide) includes pediatric dosing in the FDA approved labeling.8,9 FDA review packages were not available for this medication. Warnings for the use of Aristospan® and Kenalog-10® in pediatric patients due to the presence of benzyl alcohol have been described above (see table 1).

Adverse events for Aristospan® and Kenalog-10® were similar to those listed in general for corticosteroids (see above) with the addition of: dry scaly skin, glycosuria, hypertrichosis, calcinosis (following intra-articular or intralesional use), postinjection flare (following intra-articular use), rare instances of blindness associated with periocular injections, and decreased resistance to infection.8,9 FDA medical review packages were not available for these medications.

**Celestone Soluspan® (betamethasone)**

Adverse event data for Celestone Soluspan® was gathered from the package insert.10 FDA approval packages were not available for review.

Adverse events for Celestone Soluspan® were similar to those listed in general for corticosteroids (see above) with the addition of: dry scaly skin, glycosuria, hypertrichosis, negative nitrogen balance due to protein catabolism, calcinosis (following intra-articular or intralesional use), postinjection flare (following intra-articular use), rare instances of blindness associated with periocular injections, and decreased resistance to infection.10 The following adverse events have been reported for general corticosteroids but were **NOT** included as adverse events for Celestone Soluspan®: manifestations of latent diabetes mellitus and menstrual irregularities.
Elocon® (mometasone furoate)

The use of this medication in pediatric patients (≥2 years) is recommended for less than 3 weeks. 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 HPA axis suppression, Cushing’s syndrome, adrenal insufficiency upon withdraw, skin atrophy, striae, linear growth retardation, delayed weight gain, and intracranial hypertension are more likely to occur in pediatric patients.

The adverse event data for Elocon® was obtained from the package insert. FDA approval packages were not available for this medication. The package insert notes that rates of adverse events may differ in clinical practice because clinical trials for Elocon® were conducted under variable conditions. In pediatric studies (n=74), 7% of patients experienced adverse events including: stinging, pruritus, and furunculosis. In a pediatric trial, 24 patients (age 6 to 23 months) used Elcon® cream for 3 weeks covering a mean body surface area of 41%. Sixteen percent of patients reported HPA axis suppression after treatment. Additional adverse events reported in pediatric (age 6 months to 2 years) trials (n=182) included: decreased glucocorticoid levels (2), paresthesia (2), folliculitis (1) moniliasis (1), bacterial infection (1), skin depigmentation (1). Ninety seven patients, participating in a clinical trial, experienced skin atrophy including: shininess (4), telangiectasia (1), loss of elasticity (4), loss of normal skin markings (4), thinness (1), and bruising (1). Adverse events that have been reported for topical corticosteroids in general include: irritation, dryness, folliculitis, hypertrichosis, acneiform eruptions, hypopigmentation, perioral dermatitis, allergic contact dermatitis, secondary infection, striae, and miliaria.

Aldara® (imiquimod), Zyclara® (imiquimod)

Package inserts and original FDA approval packages were utilized to gather safety information for these medications.

It has been reported that the pediatric patients applying Aldara® for molluscum contagiosum experienced application site reactions most often. Additional adverse events reported in these trials were similar to those reported in adult patient with the addition of: otitis media (5%) and conjunctivitis (3%). Local skin reactions reported in pediatric patients and considered severe include: erythema (28%), edema (8%), scabbing/crusting (5%), flaking/scaling (5%), erosion (2%) and weeping/exudate (2%).

The Aldara® package insert notes that rates of adverse events may differ in clinical practice because clinical trials were conducted under variable conditions. The following adverse events were reported in >1% of adult patients applying Aldara® to the face or scalp 2 times a week for 16 weeks for actinic keratosis (n=215): application site reaction: 71 (33%), upper respiratory tract infection: 33 (15%), sinusitis: 16 (7%), headache: 11 (5%), carcinoma squamous: 8 (4%), diarrhea: 6 (3%), eczema: 4 (2%), back pain: 3 (1%), fatigue: 3 (1%), atrial fibrillation: 3 (1%), viral infection: 3 (1%), dizziness: 3 (1%), vomiting: 3 (1%), UTI: 3 (1%), fever: 3 (1%), rigors: 3 (1%), and alopecia: 3 (1%). Specific application site reactions that were reported in >1% of adult patients taking Aldara® for actinic keratosis (n=215) included: itching: 44 (20%), burning: 13 (6%), bleeding: 7 (3%), stinging: 6 (3%), pain: 6 (3%), induration: 5 (2%), tenderness: 4 (2%), and irritation: 4 (2%). The following local skin reactions have been reported in adult patients applying Aldara® for actinic keratosis (n=215): erythema (all grades): 209 (97%), erythema (severe): 38 (18%), flaking/scaling/dryness (all grades): 199 (93%), flaking/scaling/dryness (severe): 16 (7%), scabbing/crusting (all grades): 169 (79%), scabbing/crusting (severe): 18 (8%), edema (all grades): 106 (49%), erosion/ulceration (all
grades): 103 (48%), erosion/ulceration (severe): 5 (2%), weeping/exudate (all grades): 45 (22%), and vesicles (all grades): 19 (9%). Increased scarring scores were reported in 2.9% (6/206) patients with a baseline and 8-week post treatment scarring assessment.

In patients applying Aldara® for genital warts, female patients reported severe skin reactions including: erythema (3%), ulceration (2%), and edema (1%); and for males, erosion (2%), and erythema (1%), edema (1%), induration (1%), and excoriation/flaking (1%). The following adverse reactions were reported by >1% of patients: burning, hypopigmentation, irritation, itching, pain, rash, sensitivity, soreness, stinging, tenderness, bleeding, burning, itching, pain, tenderness, tinea cruris, fatigue, fever, influenza-like symptoms, headache, diarrhea and myalgia. Aldara® was studied in male and female patients (n=784) aged 15-77 (mean age 31.5) with genital warts. Patients applied Aldara® three times a week for 16 weeks. Some patients were treated for up to 32 weeks if their warts were not cleared after the initial 16 week treatment. Common adverse events reported in >2% of patients included: application site reactions 26.7%, infection 3.8%, upper respiratory infection 3.3%, headache 2.5%, fatigue 2.1%, nausea 2.1%, herpes simplex 2.1%, and myalgia 2.0%. In a similar study of male and female patients (n=943) age 16-78 (mean 31.2) with genital warts, adverse events reported in >2% of patients included: application site reactions 27.7%, infection 4.5%, headache 2.9%, respiratory infection 2.1%, and myalgia 2%.

Similar to the Aldara® package insert, Zyclara® adverse events may differ in clinical practice because clinical trials were conducted under variable conditions. Adult patients with actinic keratosis completing clinical trials applied Zyclara® daily for 2 weeks to their entire face or blading scalp. Treatment cycles were separated by 2 weeks of no treatment. Adverse reactions reported in clinical trials are listed below (see table 5). In addition to the adverse events included in the chart, the following events have been reported: application site bleeding, application site swelling, chills, dermatitis, herpes zoster, insomnia, lethargy, myalgia, pancytopenia, pruritus, squamous cell carcinoma, and vomiting.

Table H-5: Zyclara® Adverse Event Data

<table>
<thead>
<tr>
<th>Adverse Events reported in &gt;2% of Patients</th>
<th>Zyclara® 2.5% (n=160)</th>
<th>Zyclara® 3.75% (n=160)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Headache</strong></td>
<td>3(2%)</td>
<td>10(6%)</td>
</tr>
<tr>
<td><strong>Application site pruritus</strong></td>
<td>6(4%)</td>
<td>7(4%)</td>
</tr>
<tr>
<td><strong>Fatigue</strong></td>
<td>2(1%)</td>
<td>7(4%)</td>
</tr>
<tr>
<td><strong>Nausea</strong></td>
<td>1(1%)</td>
<td>6(4%)</td>
</tr>
<tr>
<td><strong>Influenza like illness</strong></td>
<td>6(4%)</td>
<td>1(&lt;1%)</td>
</tr>
<tr>
<td><strong>Application site irritation</strong></td>
<td>4(3%)</td>
<td>5(3%)</td>
</tr>
<tr>
<td><strong>Pyrexia</strong></td>
<td>0</td>
<td>5(3%)</td>
</tr>
<tr>
<td><strong>Anorexia</strong></td>
<td>0</td>
<td>4(3%)</td>
</tr>
<tr>
<td><strong>Dizziness</strong></td>
<td>1(&lt;1%)</td>
<td>4(3%)</td>
</tr>
<tr>
<td><strong>Herpes simplex</strong></td>
<td>0</td>
<td>4(3%)</td>
</tr>
<tr>
<td><strong>Application site pain</strong></td>
<td>2(1%)</td>
<td>5(3%)</td>
</tr>
<tr>
<td><strong>Lymphadenopathy</strong></td>
<td>4(3%)</td>
<td>3(2%)</td>
</tr>
<tr>
<td><strong>Oral herpes</strong></td>
<td>4(3%)</td>
<td>0</td>
</tr>
<tr>
<td><strong>Arthralgia</strong></td>
<td>4(3%)</td>
<td>2(1%)</td>
</tr>
<tr>
<td><strong>Cheilitis</strong></td>
<td>3(2%)</td>
<td>0</td>
</tr>
<tr>
<td><strong>Diarrhea</strong></td>
<td>2(1%)</td>
<td>3(2%)</td>
</tr>
<tr>
<td><strong>Local Skin Reactions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Erythema</strong></td>
<td>96%</td>
<td>96%</td>
</tr>
<tr>
<td><strong>Severe erythema</strong></td>
<td>14%</td>
<td>25%</td>
</tr>
<tr>
<td><strong>Scabbing/Crusting</strong></td>
<td>84%</td>
<td>93%</td>
</tr>
</tbody>
</table>
An additional database review of Zyclara® (n=779) across two clinical trials, revealed the following adverse events reported in >1% of patients (see table 6).25

<table>
<thead>
<tr>
<th></th>
<th>Zyclara® 3.75% (n=400)</th>
<th>Zyclara® 2.5% (n=379)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Application site pain</td>
<td>28 (7.0%)</td>
<td>20 (5.3%)</td>
</tr>
<tr>
<td>Application site irritation</td>
<td>24 (6.0%)</td>
<td>13 (3.4%)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>16 (4.0%)</td>
<td>21 (5.5%)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>12 (3.0%)</td>
<td>7 (1.8%)</td>
</tr>
<tr>
<td>Application site pruritus</td>
<td>11 (2.8%)</td>
<td>17 (4.5%)</td>
</tr>
<tr>
<td>Headache</td>
<td>9 (2.3%)</td>
<td>8 (2.1%)</td>
</tr>
<tr>
<td>Vaginitis bacterial</td>
<td>8 (2.0%)</td>
<td>6 (1.6%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>7 (1.8%)</td>
<td>4 (1.1%)</td>
</tr>
<tr>
<td>Back pain</td>
<td>7 (1.8%)</td>
<td>4 (1.1%)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>6 (1.5%)</td>
<td>6 (1.6%)</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>6 (1.5%)</td>
<td>4 (1.1%)</td>
</tr>
<tr>
<td>Sinus congestion</td>
<td>6 (1.5%)</td>
<td>1 (0.3%)</td>
</tr>
<tr>
<td>Cough</td>
<td>5 (1.3%)</td>
<td>5 (1.3%)</td>
</tr>
<tr>
<td>Rash</td>
<td>5 (1.3%)</td>
<td>2 (0.5%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>5 (1.3%)</td>
<td>1 (0.3%)</td>
</tr>
<tr>
<td>Skin laceration</td>
<td>5 (1.3%)</td>
<td>1 (0.3%)</td>
</tr>
</tbody>
</table>

In patients applying Zyclara® 3.75% for genital warts (n=400) for up to 8 weeks, adverse events occurring in greater than ≥2% included: application site pain: 28 (7%), application site irritation: 24 (6%), application site pruritus: 11 (3%), vaginitis bacterial: 6/216 (3%), and headache: 6(2%). Additional local skin reactions that required medical attention, caused patients to discontinue the study or extended beyond the treatment area included: erythema (mild, moderate or severe): 70%, severe erythema: 9%, edema (mild, moderate or severe): 41%, severe edema: 2%, erosion/ulceration (mild, moderate or severe): 36%, severe erosion/ulceration: 11%, exudate (mild, moderate or severe): 34%, and severe exudate: 2%. In addition to the adverse events included above, these events have been reported: rash, back pain, application site rash, application site cellulitis, application site excoriation, application site bleeding, scrotal pain, scrotal erythema, scrotal ulcer, scrotal edema, sinusitis, nausea, pyrexia, and influenza-like symptoms.

Adverse events reported for Zyclara® from the sponsor’s clinical trial safety database include: anginal pain (angia pectoris, prinzmetal angina): 3 (Rate=0.035%), arrhythmia: 15 (Rate=0.177%), ventricular arrhythmia: 2 (Rate=0.024%), cardiac arrest: 1 (Rate=0.012%), cardiac failure: 7 (Rate=0.083%), chest pain: 12 (Rate=0.142%), dizziness: 66 (Rate=0.780%), dyspnea: 2 (Rate=0.024%), fibrillation atrial: 12 (Rate=0.142%), hypotension: 2 (Rate=0.024%),
acute myocardial infarction: 3 (Rate=0.035%), palpitation: 9 (Rate=0.106%), pulmonary edema: 1 (Rate=0.012%), syncope: 7 (Rate=0.083%), tachycardia: 8 (Rate=0.095%), presyncope: 1 (Rate=0.012%), and tachycardia ventricular: 2 (Rate=0.024%).\textsuperscript{24} It is important to note that the original FDA approval document only contains data for adult patients. Across five clinical trials, patients applying the medication for 2 to 3 week cycles (n=665) experienced the following adverse events most often: headache, local site reactions, fatigue and nausea. Patients using the higher dose (3.75%) of Zyclara experienced local site reactions more often.

Two clinical trials assessing the use of Zyclara® 2.5% and 3.75% in adult patients with actinic keratosis were submitted in the original FDA approval document.\textsuperscript{24} Patients age 36 to 90 applied the medication using one of two treatment cycles: 1) 3 weeks of treatment followed by 3 weeks of rest, 2) 3 weeks of treatment followed by 8 weeks of rest. Adverse events reported most often in patients applying Zyclara® included: application site adverse events, fatigue, headache, lymphadenopathy and influenza like illness.

**Serious Adverse Events**

Aldara® was studied in male and female patients (n=784) aged 15-77 (mean age 31.5) with genital warts. Patients applied Aldara® three times a week for 16 weeks.\textsuperscript{25} Some patients were treated for up to 32 weeks if their warts were not cleared after the initial 16 weeks. Serious adverse events reported in this study included: acute appendicitis (1), skull fracture (1), increased depression/suicide attempt (1), suicide attempt/drug overdose (1), inferior myocardial infarction (1), pyelonephritis (1), pacemaker generator exchange (1), pancreatitis (1), cervical cancer (1), exacerbation of depression (1), incomplete abortion (1), possible infection of GI tract (1), and heroin addiction (1). In a similar study of male and female patients (n=943) age 16-78 (mean 31.2) with genital warts, 14 patients experienced serious adverse events including: alteration in speech and sensation of spaciness (1), fracture of left clavicle (1); exacerbation of eczema at non-wart site (1), rectal pain due to internal warts-remote site (1), nephrotic syndrome (1), carcinoma of vulva (1), vulval pain (with anorexia and fatigue) (1), depression (1), lymphangitis due to dog bite (1), axillary abscess (1), laryngeal cancer (1), vomiting and abdominal pain (1), cholecystectomy (1), flu (1), tonsil abscess (1), metrorrhagia (1), and act fetal distress (1).

The first clinical trial reviewed in the original FDA approval document for Zyclara® (GW01-0702) had 227 patients complete the study.\textsuperscript{24} Severe adverse events reported in patients applying the 3.75% cream included: cerebrovascular accident, gout, and atrial fibrillation. Severe adverse events reported in patients applying the 2.5% cream included: oral herpes, sinusitis, pneumonia, application site infection, bacterial pneumonia, application site irritation, pruritic rash, procedural pain, and cartilage injury. The second clinical trial (GW01-704) reported the following severe adverse events in patients applying the 3.75% cream: influenza-like illness, chest pain, diarrhea, vascular graft, and anxiety. Severe adverse events reported in patients applying the 2.75% cream included: bronchiectasis, influenza-like illness twice, cheilitis, lymphadenopathy twice, angina pectoris, atrial fibrillation, and arteriosclerosis.

Serious Adverse events reported across trials (n=160) of adult patients (mean age 64.4) applying Zyclara® 2.5% cream for 2 weeks included: atrial fibrillation (1), chest pain (1), pneumonia (2), acute myocardial infarction (1), non-cardiac chest pain (1), and ventricular tachycardia (1).\textsuperscript{24} Events reported in adult patients (n=160) applying Zyclara® 3.75% cream for 2 weeks included: cerebrovascular accident (1), atrial fibrillation (1), small intestine obstruction (1), chest pain (1), anxiety (1), and diarrhea (1).
Serious Adverse events reported across trials (n=160) of adult patients (mean age 64.7) applying Zyclara® 2.5% cream for 3 weeks included: chest pain (1), pneumonia (1), aortic valve stenosis (1), syncope (1), and bronchitis (1).24 Events reported in adult patients (n=160) applying Zyclara® 3.75% cream for 3 weeks included: pneumonia (1), breast cancer (1), surgery (1), dyspnea (1), hip fracture (1), arthralgia (1), wound infection (1), coronary artery disease (1), Non Hodgkin lymphoma (1), and pancytopenia (1).

An additional database review of Zyclara® (n=779) across two clinical trials revealed the following severe adverse events (see table 7).25

Table H-7: Severe Adverse Events Reported in Patients Applying Zyclara®

<table>
<thead>
<tr>
<th>Event</th>
<th>Zyclara® 3.75% (n=400)</th>
<th>Zyclara® 2.5% (n=379)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Application site pain</td>
<td>6 (1.5%)</td>
<td>5 (1.3%)</td>
</tr>
<tr>
<td>Application site irritation</td>
<td>2 (0.5%)</td>
<td>3 (0.8%)</td>
</tr>
<tr>
<td>Application site reaction</td>
<td>1 (0.3%)</td>
<td>3 (0.8%)</td>
</tr>
<tr>
<td>Application site pruritus</td>
<td>1 (0.3%)</td>
<td>2 (0.5%)</td>
</tr>
<tr>
<td>Application site rash</td>
<td>2 (0.5%)</td>
<td>0</td>
</tr>
<tr>
<td>Application site dermatitis</td>
<td>0</td>
<td>1 (0.3%)</td>
</tr>
<tr>
<td>Application site erythema</td>
<td>0</td>
<td>1 (0.3%)</td>
</tr>
<tr>
<td>Application site ulcer</td>
<td>0</td>
<td>1 (0.3%)</td>
</tr>
<tr>
<td>Application site vesicles</td>
<td>1 (0.3%)</td>
<td>0</td>
</tr>
<tr>
<td>Chest pain</td>
<td>1 (0.3%)</td>
<td>0</td>
</tr>
<tr>
<td>Influenza like illness</td>
<td>1 (0.3%)</td>
<td>0</td>
</tr>
<tr>
<td>Pelvic mass</td>
<td>1 (0.3%)</td>
<td>0</td>
</tr>
<tr>
<td>Infections and infestation</td>
<td>3 (0.8%)</td>
<td>3 (1.1%)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>1 (0.3%)</td>
<td>1 (0.3%)</td>
</tr>
<tr>
<td>Application site infection</td>
<td>0</td>
<td>1 (0.3%)</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>0</td>
<td>1 (0.3%)</td>
</tr>
<tr>
<td>Influenza</td>
<td>1 (0.3%)</td>
<td>0</td>
</tr>
<tr>
<td>Pharyngitis streptococcal</td>
<td>0</td>
<td>1 (0.3%)</td>
</tr>
<tr>
<td>Vaginal infection</td>
<td>1 (0.3%)</td>
<td>0</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>3 (0.8%)</td>
<td>2 (0.5%)</td>
</tr>
<tr>
<td>Acute abdomen</td>
<td>1 (0.3%)</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>0</td>
<td>1 (0.3%)</td>
</tr>
<tr>
<td>Haemorrhoidal haemorrhage</td>
<td>1 (0.3%)</td>
<td>0</td>
</tr>
<tr>
<td>Haemorrhoids</td>
<td>0</td>
<td>1 (0.3%)</td>
</tr>
<tr>
<td>Proctalgia</td>
<td>1 (0.3%)</td>
<td>0</td>
</tr>
<tr>
<td>Reproductive system and breast disorders</td>
<td>4 (1.0%)</td>
<td>2 (0.5%)</td>
</tr>
<tr>
<td>Scrotal erythema</td>
<td>2 (0.5%)</td>
<td>1 (0.3%)</td>
</tr>
<tr>
<td>Dysmenorrhea</td>
<td>2 (0.5%)</td>
<td>0</td>
</tr>
<tr>
<td>Vulval ulceration</td>
<td>0</td>
<td>1 (0.3%)</td>
</tr>
<tr>
<td>Injury, poisoning and procedural complications</td>
<td>1 (0.3%)</td>
<td>1 (0.3%)</td>
</tr>
<tr>
<td>Gunshot wound</td>
<td>1 (0.3%)</td>
<td>0</td>
</tr>
<tr>
<td>Upper limb fracture</td>
<td>0</td>
<td>1 (0.3%)</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>0</td>
<td>1 (0.3%)</td>
</tr>
<tr>
<td>Groin pain</td>
<td>0</td>
<td>1 (0.3%)</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>1 (0.3%)</td>
<td>1 (0.3%)</td>
</tr>
<tr>
<td>Headache</td>
<td>1 (0.3%)</td>
<td>0</td>
</tr>
<tr>
<td>Migraine</td>
<td>0</td>
<td>1 (0.3%)</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>1 (0.3%)</td>
<td>0</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>1 (0.3%)</td>
<td>0</td>
</tr>
<tr>
<td>Iron deficiency anemia</td>
<td>0</td>
<td>1 (0.3%)</td>
</tr>
<tr>
<td>Tooth extraction</td>
<td>1 (0.3)</td>
<td>0</td>
</tr>
</tbody>
</table>
Discontinuations

Patients utilizing Aldara® for actinic keratosis withdrew from studies or initialed rest periods most often due to application site reactions and local skin reactions. Specifically, 2% (5/215) of patients discontinued due to application site reactions. Rest periods occurred in 16% (35/215), 11% (17/160), and 7% (11/160) of patients using Aldara®, Zyclara® 3.75% and Zyclara® 2.5% cream respectively. Four out of 327 (1.2%) patients applying Aldara® and 3 out of 400 (1%) patients applying Zyclara® for genital warts reported discontinuing due to local skin/application reactions. Thirty-two percent (126/400) of patients taking Zyclara® temporarily discontinued treatment due to local skin reactions.

Aldara® was studied in male and female patients (n=784) aged 15-77 (mean age 31.5) with genital warts. Patients applied Aldara® three times a week for 16 weeks. Some patients were treated for up to 32 weeks if their warts were not cleared after the initial 16 weeks. Patients discontinued due to the following adverse events: intolerable local skin reactions: burning, tenderness, itching, pain (31); flu-like symptoms (2); fatigue (1); bacterial infection at the wart site (1); urethral irritation (1); and intraepithelial vulvar neoplasia (1). In a similar study of male and female patients (n=943) age 16-78 (mean 31.2) with genital warts, 105 patients discontinued due to an adverse event including: local site reaction: burning, tenderness, itching, and pain (89); flu-like symptoms (8); headache, chills and fever (3); worsening of psoriasis (1); generalized itching (1); diarrhea (1); vaginal candidiasis (1); and fatigue (1).

Out of the 227 patients applying Zyclara® and completed the GW01-0702 trial, two withdrew from the treatment due to safety reasons: tachycardia, chest pain, hypertension, and increased tremors.

Post-marking Adverse Events

Additional adverse events identified after Aldara® and Zyclara® were brought to the market include: tingling at the application site, angioedema, capillary leak syndrome, cardiac failure, cardiomyopathy, pulmonary edema, arrhythmias (tachycardia, atrial fibrillation, palpitations), chest pain, ischemia, myocardial infarction, syncope, thyroiditis, abdominal pain, decreases in red cell, white cell and platelet counts (including idiopathic thrombocytopenic purpura), lymphoma, abnormal liver function, herpes simplex, arthralgia, agitation, cerebrovascular accident, convulsions (including febrile convulsions), depression, insomnia, multiple sclerosis aggravation, paresis, suicide, dyspnea, proteinuria, dysuria, urinary retention, exfoliative dermatitis, erythema multiforme, hyper/hypo pigmentation, hypertrophic scar, and Henoch-Schönlein purpura syndrome. Post-marketing data was gathered by the sponsor in 2004 and was included in the Zyclara® original FDA approval document. Adverse reported include: chest pain (2), angina (1), myocardial infarction (1), tachycardia (2), syncope (2), palpitation (1), sudden death (1) (potentially due to arrhythmia), atrial fibrillation (1).

Tenormin® (atenolol)

Tenormin® is not FDA approved for use in pediatric patients and therefore safety data in this population is not available. The adverse event data provided below was gathered from the Tenormin® package insert and is specific for adult hypertensive patients. Adverse events specific for patients using this medication for acute myocardial infarction was not included in this analysis.

Controlled studies in conducted in the United States and in unspecified foreign countries revealed the following adverse events associated with atenolol (n=399): bradycardia (3%), cold extremities (12%), postural hypotension (4%), leg pain (3%), dizziness (13%), vertigo (2%),
light-headedness (3%), tiredness (26%); fatigue (6%), lethargy (3%), drowsiness (2%), depression (12%); dreaming (3%), diarrhea (3%), nausea (3%), wheeziness (3%), and dyspnea (6%).

Adverse events reported for beta-adrenergic blocking agents in general include: agranulocytosis; fever, combined with aching and sore throat, laryngospasm, and respiratory distress; reversible mental depression progressing to catatonia; acute reversible syndrome characterized by disorientation of time and place; short-term memory loss; emotional lability with slightly clouded sensorium; decreased performance on neuropsychometrics; mesenteric arterial thrombosis, ischemic colitis, erythematous rash; skin rashes and/or dry eyes.

Post-marketing Adverse Events
Additional adverse events revealed during post-marketing surveillance include: dry mouth, headache, elevated liver enzymes and/or bilirubin, hallucinations, impotence, purpura, reversible alopecia, Peyronie's disease, postural hypotension which may be associated with syncope, psoriasiform rash or exacerbation of psoriasis, psychoses, thrombocytopenia, visual disturbance, sick sinus syndrome, development of antinuclear antibodies (ANA), lupus syndrome, and Raynaud’s phenomenon.

Timoptic® (timolol maleate), Timoptic-XE® (timolol maleate), Betimol® (timolol)
Timoptic®, Timoptic-XE®, and Betimol® are not FDA approved for use in pediatric patients and therefore safety data in this population is not available. The adverse event data provided below is gathered from the package inserts for these medications and is specific for adult patients. These medications are ophthalmic preparations and therefore many of the common adverse events are associated with the ophthalmic route of administration. One in eight patients reported stinging and burning after administration of all three of these medications.

In patients taking Timoptic-XE®, one in three patients, in clinical trials, experienced blurred vision upon drop administration lasting 30 seconds to 5 minutes. One in eight patients reported stinging and burning after use. Additional adverse events reported in 1-5% of patients included: pain, conjunctivitis, discharge (e.g., crusting), foreign body sensation, itching and tearing, headache, dizziness, and upper respiratory infections.

In patients taking Betimol® 0.25% or 0.5%, adverse events that occurred more than 5% in two controlled clinical studies (n=184 patients) included: dry eyes, itching, foreign body sensation, discomfort in the eye, eyelid erythema, conjunctival injection, and headache. Adverse events occurring at a frequency of 1-5% included: eye pain, epiphora, photophobia, blurred or abnormal vision, corneal fluorescein staining, keratitis, blepharitis and cataract, allergic reaction, asthenia, common cold and pain in extremities, hypertension, nausea, peripheral edema, dizziness, dry mouth, respiratory infection and sinusitis. Additional adverse events reported in ophthalmic use of beta-blockers include: blepharoptosis, retinal vascular disorder, bronchospasm.

The following adverse events were reported in the package inserts of both Timoptic® and Timoptic-XE®: headache; asthenia/fatigue; arrhythmia; hypertension; worsening of angina pectoris; pulmonary edema; edema; claudication; Raynaud's phenomenon; cold hands and feet; nausea; dyspepsia; anorexia; dry mouth; systemic lupus erythematosus; dizziness; somnolence; insomnia; nightmares; behavioral changes and psychic disturbances including confusion, hallucinations, anxiety, disorientation, nervousness, and memory loss; alopecia and psoriasiform rash or exacerbation of psoriasis; signs and symptoms of systemic allergic reactions, including anaphylaxis, and angioedema; cough and upper respiratory infections; signs and symptoms of
ocular irritation including blepharitis, keratitis, ocular pain, discharge (e.g., crusting), foreign body sensation, itching and tearing, and dry eyes; ptosis; cystoid macular edema; visual disturbances including refractive changes and diplopia; pseudopemphigoid; choroidal detachment following filtration surgery; tinnitus; retroperitoneal fibrosis; decreased libido; and Peyronie's disease.\textsuperscript{15,16}

Adverse events reported for Betimol®, Timpotic®, Timoptic-XE® included: conjunctivitis, decreased corneal sensitivity, visual disturbances including refractive changes and diplopia, chest pain, arrhythmia, palpitation, bradycardia, hypotension, syncope, heart block, cerebral vascular accident, cerebral ischemia, cardiac failure, cardiac arrest, masked symptoms of hypoglycemia in diabetic patients, diarrhea, depression, impotence, increase in signs and symptoms of myasthenia gravis and paresthesia, dyspnea, bronchospasm (predominantly in patients with preexisting bronchospastic disease), respiratory failure, nasal congestion; alopecia, urticaria, and localized/generalized rash.\textsuperscript{15-17}

Adverse events reported for oral timolol and oral beta-blocking agents that could be considered potential adverse events for ophthalmic timolol include: erythematous rash; fever combined with aching and sore throat; laryngospasm with respiratory distress; extremity pain; decreased exercise tolerance; weight loss; worsening of arterial insufficiency; vasodilatation; gastrointestinal pain; hepatomegaly; vomiting; mesenteric arterial thrombosis; ischemic colitis; nonthrombocytopenic purpura; thrombocytopenic purpura; agranulocytosis; hyperglycemia; hypoglycemia; pruritus; skin irritation; increased pigmentation; sweating; arthralgia; vertigo; local weakness; diminished concentration; reversible mental depression progressing to catatonia; an acute reversible syndrome characterized by disorientation for time and place; emotional lability; slightly clouded sensorium; and decreased performance on neuropsychometrics; rales; bronchial obstruction; urination difficulties.\textsuperscript{15,16}
References