Infantile hemangiomas, which occur in about 4% to 5% of all children, create a difficult management dilemma in routine pediatric practices and continue to stir debate and controversy. Practitioners are aware that all elevated hemangiomas and most flat hemangiomas typically grow throughout the first year of life, and that most elevated ones spontaneously involute over the next 5 to 10 years. The flat, less conspicuous hemangiomas often do not. Nonetheless, why should a clinician be concerned about these benign lesions?

I think it may become incumbent upon the pediatric community to alter their approach to most hemangiomas. At birth, 65% of hemangioma precursors were present. A recent photographic report showed that the most rapid growth of hemangiomas occurred between age 5.5 weeks and age 7.5 weeks. This age factor may be critical when deciding upon using a more prophylactic type of treatment, such as propanolol, because most children with hemangiomas are not referred to a dermatologist until age 5 months. These authors have even suggested biweekly monitoring for any high-risk hemangiomas, such as those listed in Sidebar 1 (see page 231), after the first month of age.

Although the lesions are always benign and usually self-limited, some of them may be located in areas that become life-threatening or function-threatening, some may ulcerate and bleed, and some may lead to significant psychosocial distress or may cause permanent residual skin changes that are cosmetically undesirable. Importantly, clinicians cannot reliably predict which hemangiomas in the first few months are going to create any of these problems. In addition, one must be very diligent about the further evaluation of children with possible PHACE syndrome or multiple hemangiomatosis, as additional expert consultation will be needed.

CATEGORIZATION OF INFANTILE HEMANGIOMAS

Infantile hemangiomas are generally classified as focal, segmental, or indeterminate, and then subcategorized further into superficial, mixed, or deep. Tollefson et al scored hemangiomas based on intensity of color, degree of elevation, and distortion of local landmarks. These parameters could be helpful for pediatricians too. I recommend that pediatricians read the entire electronic version of their article in August 2012 issue of Pediatrics for further edification as to whether and when to initiate therapy. I initially missed the true impact of this article because I rely more heavily on the paper version of the journal.

For the practitioner, it is the numerous smaller hemangiomas, the less conspicuous ones, or the more cosmetically subtle but noticeable hemangiomas that can create difficult psychosocial or emotional dilemmas for parents and practitioners when deciding upon whether to treat. Hindsight is always much better, and once again, as with other more cosmetic conditions such as plagiocephaly, early timing of therapy may be much more critical than previously widely believed. It is also much more difficult to be prescient about the severity or complexity of these types of hemangiomas.

Although treatment timing and therapeutic choices have been completely revolutionized in the past 4 years with the use...
of propanolol, they still remain controversial. Before 2008, corticosteroids and laser therapy had been the mainstay of treatment for life-threatening, functioning-threatening, complicated, or difficult lesions. However, most other types of hemangiomas have been “treated” with benign neglect, knowing that most would eventually spontaneously involute and dissipate by 6 to 10 years of age, leaving only minor or no residual signs.

But is this last assumption true? Nearly 75% of nodular hemangiomas reportedly create discernible residual skin changes. The growth rate of hemangiomas is unpredictable and quite variable, and 12% are significantly complex. Adding to the clinicians’ consternation, no pharmacologic agents have been approved by the US Food and Drug Administration for the treatment of infant hemangiomas; no consensus guidelines from pediatric groups were available prior to 2013; and very few randomized control trials comparing the newest therapy, propanolol, with placebo have been published.

**USE OF PROPANOLOL IN OUTPATIENT SETTINGS**

Overall, propanolol appears to be a very safe drug to use in infants. It certainly is much safer than long-term treatment with corticosteroids, vincristine, or methotrexate; and it is much more tolerable and inexpensive than laser therapies. In the past, most practitioners had used propanolol in at least a few infants who had supraventricular tachycardia. But for these patients, propanolol therapy has usually been initiated in an inpatient setting under cardiac monitoring. For routine infantile hemangiomas, we have begun to initiate propanolol treatment in healthy children without cardiac disease in outpatient settings.

Nearly 48 (56%) of the 85 articles evaluated by Drolet et al observed no complications with propanolol use in any patient. Ensuing articles have subsequently reported occasional occurrences of hypotension, hypoglycemia, restless sleep, constipation, and very rarely hypokalemia or adrenergic blockade (worsening asthma). Most of these adverse events were “infrequent and asymptomatic.” In contrast, Hermans et al recently reported somewhat higher rates for adverse effects (possible “background noise”) over an average of 10 months of therapy for hypotension (3.4%), nocturnal restlessness (22.4%), cold extremities (36.2%), and wheezing (9.2%). This study had no control population, only 1 patient discontinued therapy, and the dose was reduced in 8% of children.

In 3 prospective studies of propanolol, the only clinically recognizable adverse events were cold extremities and prolonged capillary refill. The most worrisome — albeit rare — serious concern with initiation of propanolol treatment, even with lower doses, is hypoglycemia and/or hypoglycemic seizures. But the few reported incidents were often associated with “poor oral intake or concomitant infection.” It is important to remember that propanolol may mask some of the major symptoms of hypoglycemia, such as shakiness, anxiety, and hunger. Thus, parents should be advised that increased sweating is thought to be the most reliable and prominent symptom of hypoglycemia in infants before they develop more worrisome symptoms such as lethargy, poor feeding, and seizures.

**Other Precautions with Propanolol**

The recent use (within a few weeks) of corticosteroids is believed to place these infants at potential increased risk for hypoglycemia as well. Temporary discontinuation of propanolol may be prudent during any viral illness associated with reduced oral intake, wheezing, or moderately severe cough (the only sign parents may have of a wheezing infant) (see Sidebar 2). Giving the dose of medication with or after meals may be advisable. Frequent feeding during the night for young infants or preterm infants is suggested as well.

Inpatient monitoring is advised for those who have PHACE syndrome; those with comorbid conditions of the cardiovascular, respiratory, or endocrine systems; those with visceral hemangiomas; and for those younger than 2 months or 48 weeks corrected gestational age.

**Initiation of Propanolol Therapy**

Outpatient monitoring for pulse and blood pressure is advised only at baseline, 1 and 2 hours after the first dose,
or with any significant increase in dose (> 0.5 mg/kg/day). Routine electrocardiogram or Holter monitoring is not indicated for otherwise healthy infants. My preference for dosing is 2 mg/kg/day divided in a twice-daily dose. This keeps all the calculations simple, easy to remember, and easy to perform for practitioners (1 mg/kg per dose) and all the dosings much simpler for parents (adherence to twice daily dosing is far superior to three-times daily dosing). I suggest follow-up at 1 week and then monthly to evaluate the hemangiomas, for adverse events, and for monitoring of pulse and blood pressure.

Subsequently, how does one decide when and whether to “pull the trigger” and when to start therapy for many of these more benign, non-threatening lesions? When does the risk-to-benefit ratio become worthwhile?  

**What to Expect with Propranolol Therapy**

The recent article by Hermans et al showed that nearly all of the 173 patients responded strikingly to propranolol therapy with a fading of abnormal color, immediate cessation of growth (a critical component of the early timing argument), softening, and rapid induction of regression. Medication was effective even though the mean age of patients was older (4.8 months old) and all of the lesions were potentially threatening or complicated.

**WHAT TO EXPECT WITH PROPRANOLOL THERAPY: A PHOTOGRAPHIC CASE**

Infantile hemangiomas are more commonly observed in white, female, and preterm infants, and those born to mothers with advanced maternal age (some apply here). The same white female infant is shown in each of the images.

The vigorous, pink, active, white female infant was born at 36 weeks gestation by spontaneous vaginal delivery with APGARS of 9/9 to a healthy 28-year old primigravida mother. The mother first noticed a small, dark, reddened, round discolored lesion on the thigh at 12 hours of age. Over the ensuing first month of age, several more red raised and flat hemangiomas had “popped up,” which were described as even bigger and redder. By age 2 months, she had about 10 hemangioma lesions present, and thus she was considered as having “infantile hemangiomatosus” (see Sidebar 1, page 231).

**Indecision About Starting Treatment**

Subsequently, she was seen in the local hematology-oncology specialty clinic for infantile hemangiomatosis, where an ultra-

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**Figure 2.** The photographs show the regression of the slightly raised focal leg hemangioma from age 4 months (A) at the initiation of treatment with propranolol (2 mg/kg/day); age 5 months (B); age 6.5 months (C); and age 9 months (D). The hemangioma sequentially faded to much less bright red, and eventually totally flattened with no more satellite metastasis after 2.5 months of treatment. The parents may want to consider further laser therapy for cosmetic reasons because these hemangiomas have a tendency not to dissipate further over time, unlike the hemangioma in Figure 1.

**Figure 3.** The photographs show the regression of the large, raised, solitary focal hemangioma and 4 brighter red hemangiomas from age 4 months (A) at the initiation of treatment with propranolol (2 mg/kg/day); age 5 months (B); age 6.5 months (C); and age 9 months (D). Each of the hemangiomas sequentially faded to much less bright red, eventually totally flattened, and developed no more satellite metastases after 5 months of treatment. This dramatic fading is a much more acceptable cosmetic result. Further laser therapy for cosmetic reasons for these proximal 3 particular focal hemangiomas will probably not be necessary as they are likely to totally disappear, and the well-faded focal ones on the sacral area are smaller, barely perceptible, and will remain covered by clothing.
sound of the liver and spleen was performed. The results were normal. The mother was told that oral propranolol therapy could be considered as an option, but it was not recommended for the patient at this point due to the lack of more serious or threatening lesions. By age 4 months, the mother noticed that the lesions on the head and back had continued to grow and proliferate (see Figures 1A and 3A). Furthermore, the surface area of the flatter lesions on the hand and leg had continued to spread (see Figures 2A and 4A).

By age 4 months, the mother had become quite alarmed at the continued rapid proliferation of the hemangiomas. She had read about their potential for low-grade re-proliferation of the hemangiomas. She had come quite alarmed at the continued rapid growth and proliferation (see Figures 1B, C, D), and hand (see Figures 4B and C) had nearly flattened completely. Most of the hemangiomas except for those on the hand were much lighter, smaller, or almost resolved over time. The hand merely appeared about half as dark red. During the last 2 months of therapy, the parents noted no more additional benefits to therapy and elected to cease the propranolol at 9 months of age. No rebound growth of the hemangiomas was observed during the month post-therapy, which has been reported elsewhere.7

When asked if they would have done anything differently, the two parents responded that they “wished they had started the propranolol at age 2 months” (and I now agree), which would have been the earliest possible time to avoid any need for monitoring in the hospital. They stated that if clinicians or parents had any concerns about the cosmetic size or locations of the lesions, they would advise physicians to initiate therapy in the child. The article by Tollefson et al2 may substantiate their concerns that the early unimpeded growth of superficial hemangiomas can lead to irreversible skin changes. They are definitely considering future laser therapy of the flat hemangiomas of the hand and leg within the next few years.8

Starting Propranolol

She was advised to have the infant’s blood pressure checked initially, at 1 and 2 hours after the first dose, or with any increased dose of medication. She was also instructed to wake the baby for a feeding at least once or twice during the night, and to particularly watch for any signs of hypoglycemia. She initiated propranolol therapy at 2 mg/kg/day divided in twice-daily doses. Drug adherence was good, as the family missed at most 1 to 2 doses monthly with the easier twice-daily dosing. With their hectic professional work schedules, thrice-daily dosing would have doomed drug adherence. Propranolol was palatable and very inexpensive. The only adverse effects they observed with the infant were occasional cold hands and feet for less than a 1-hour interval.

Beneficial Effects of Propranolol

The child received a total of 5 months of propranolol therapy, with an increased dose every 2 months in order to maintain a total dose of 2 mg/kg/day. One can see in the sequential photographs of each group of lesions at baseline (age 4 months), age 5 months, age 6.5 months, and age 9 months that the raised lesions on the head (see Figures 1B, C, D), the back (see Figures 3B, C, and D), and hand (see Figures 4B and C) had nearly flattened completely. Most of the hemangiomas except for those on the hand were much lighter, smaller, or almost resolved over time. The hand merely appeared about half as dark red. During the

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