EXPERT REVIEWS

Management of airway hemangiomas

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Airway infantile hemangiomas can cause life-threatening airway compromise from the first year of life. Diagnosis, treatment protocols and outcome measures are not standardized for this condition, making systematic assessment of treatments and outcomes difficult. This article summarizes the treatment options in use and provides an overview of their benefits and drawbacks. It also emphasizes the need for further investigation in this field and discusses the standardization that is required for such research to proceed in a useful manner. The article is divided into discussions of airway infantile hemangioma in general, medical therapy and surgical therapy. It concludes with predictions about the near future of airway infantile hemangioma research and therapy.

Keywords: airway • endoscopy • hemangioma • laser • propranolol • steroid • stridor • surgery • treatment

Pediatric vascular lesions come in many varieties, several of which can affect the airway. These lesions form two broad categories: vascular tumors, such as infantile hemangiomas (IH), and vascular malformations, such as lymphatic, arteriovenous, venous and capillary malformations. Among vascular tumors, IH are most common, affecting approximately 10% of infants, with 60% of lesions occurring in the head and neck [1,2]. IH are the most common vascular tumor to involve the airway and can occur both in isolation and as part of posterior fossa malformation, arteriovenous malformations, cardiac/aortic defects, eye anomalies and sternal defect (PHACES) syndrome [3,4]. However, airway IH (AIH) are still unusual, with most speciality pediatric hospitals treating only between one and five such lesions per year [5].

Infantile hemangiomas follow a predictable clinical course: they are generally absent at birth, enlarge during a proliferative phase in the first several months of life and gradually involute over the next several years [4]. Proliferation of IH in the infant small airway can lead to stridor and life-threatening airway compromise (**Figure 1**). The presence of AIH increases the risk of a variety of complications and predicts considerable healthcare resource use [5]. This article will provide the reader with an introduction to the therapeutic options for these unusual but dangerous lesions, considering the strengths and weaknesses of each option. A second goal is to convince the reader of the need for accurate evaluation and diagnosis including staging, systemic as opposed to local therapy, and the need to avoid multiple invasive procedures given the risks, which we will discuss, for such procedures.

Airway IH are similar to other IH on a molecular level [6], but they are worth considering separately because their effects are potentially more dangerous and therefore their management may be more urgent, and also because the airway is an anatomically and surgically unique area. While AIH are often lumped under the label 'subglottic hemangioma', they extend outside the confines of the subglottis in most cases and are better understood with further subdivision. IH occur either as focal, localized lesions, or as segmental lesions that follow a dermatomal pattern [2,7]. For unknown reasons, focal AIH have a predilection for the laryngeal airway (**Figure 2**). Here, they become symptomatic when their growth causes critical narrowing of smallest part of the infant airway, the subglottis. By contrast, segmental cutaneous IH can be associated with lesions anywhere in the upper aerodigestive tract, including contralateral sites [7]. In particular, segmental lesions occurring in the cranial nerve V3 or 'beard' distribution appear to increase the risk of lesions anywhere in the upper airway [7]. It is therefore more useful to consider AIH as a transglottic disease [8]. Focal and segmental hemangiomas also behave differently; segmental hemangiomas grow more rapidly and may have a larger intralaryngeal volume that may cause greater airway compromise depending on the location (**Figure 3**) [7,9].

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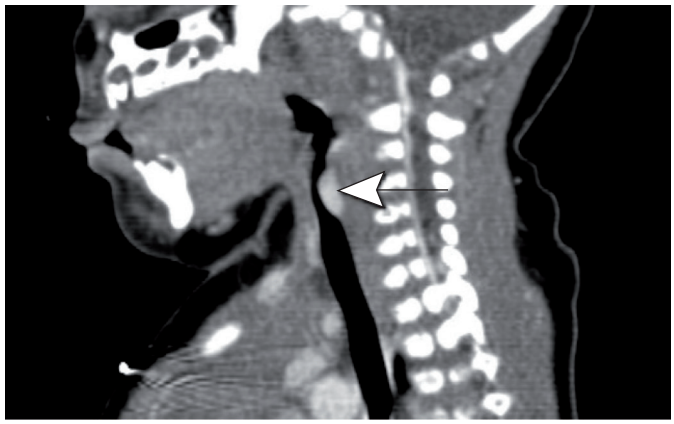

Figure 1. Sagittal computed tomography image with contrast. Arrow indicates contrast-enhancing airway infantile hemangioma in posterior subglottis.

With this understanding of AIH as a diverse and potentially life-threatening disease, many authors have proposed treatment approaches over the past few decades, often with the goal of avoiding or minimizing the need for tracheostomy. However, there are no standardized evaluation, staging and treatment protocols for AIH, leading to broad variations in management. This article aims to summarize the treatment options now in use and to provide an overview of the benefits and risks of each. It is important to note that many studies have either not explicitly described their measure of treatment success or have used different measures of success; we attempt to summarize their results in such a way as to not artificially combine results with different outcome measures. This problem arises in part because investigators have not yet developed a uniformly accepted method of evaluating and quantifying treatment outcomes.

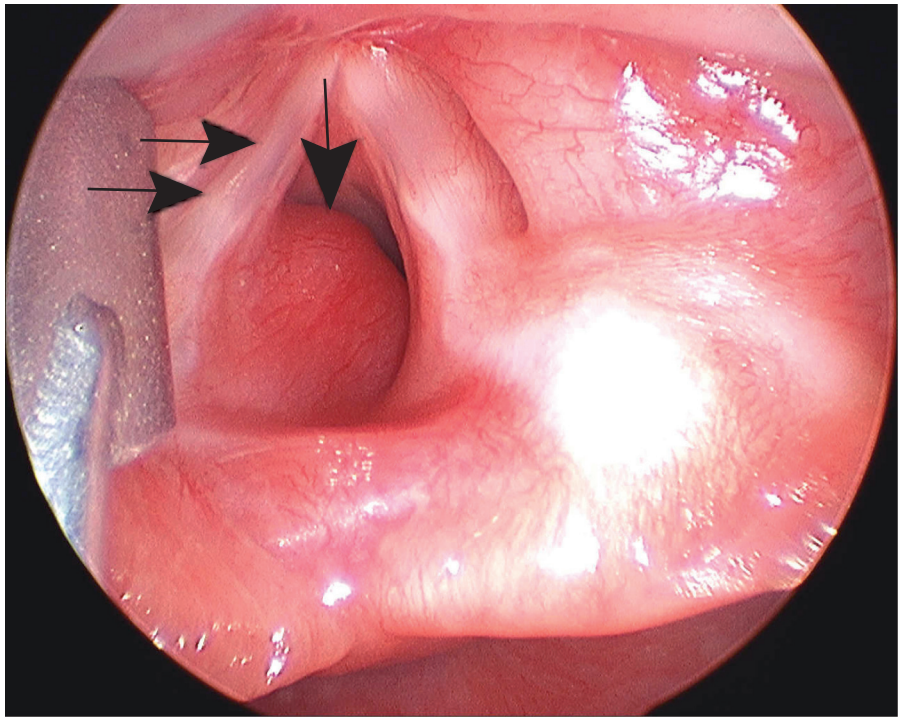

Figure 2. Endoscopic image demonstrating airway infantile hemangiomas involving the posterior glottis and subglottis with airway obstruction. Arrow indicates airway infantile hemangioma. Double arrows indicate left true vocal fold.

Medical treatment for AIH

Chemotherapy

On the basis that AIH are vascular tumors, several authors have examined the use of the presumed anti-angiogenic agents IFN-α2a and IFN-α2b. These drugs have been used particularly for lesions unresponsive to steroids and can be very effective, even in multicentric lesions and lesions refractory to other therapy [10–12]. However, interferon agents carry a high risk of potentially irreversible spastic diplegia (5–20%) [4]. This risk is particularly high in infants younger than 12 months of age [1], which is the population most at risk of airway compromise from growing AIH in the proliferative phase. It is possible that the dose of interferon may have been too high in early trials, but the possibility of irreversible spastic diplegia must be considered in its use.

Another possible chemotherapeutic agent is vincristine. This drug is used to treat some cancers and acts by interfering with the mitotic spindle. Its mechanism of action in IH is unclear, but one small study demonstrated a response to vincristine in seven out of nine patients, including five with laryngeal or tracheal lesions [13]. There are also scattered reports of single cases of IH at various locations showing response to vincristine. However, more robust studies are lacking.

Overall, chemotherapy is used in 2% or fewer of AIH patients [5]. It is important to be aware of this therapeutic option, but other choices discussed in the next sections may be more appropriate as first-line therapy.

Steroids

Both systemic and intralesional corticosteroids are common therapies for AIH. While systemic therapy is intuitively appropriate for segmental lesions, which often cover many sites [7], many practitioners simply proceed to tracheostomy in these cases. Regardless, systemic steroids may not always achieve symptom reduction in AIH [14], particularly bilateral and circumferential lesions [15]. However, the length of steroid treatment, dose-tapering protocols and outcome measures have not been standardized, so it is difficult to evaluate their effects accurately. The rate of adverse effects with systemic steroid therapy for AIH can range from 12 to 18% [14–16] and may include growth retardation, Cushing's syndrome, hypertension, gastrointestinal ulcers and pneumonia.

Another option is endoscopic intralesional injection of steroids. Used alone, intralesional steroids may not cause the same degree of systemic toxicity as systemic

steroids and appear to have a low complication rate [14]. When intralesional steroid injection is combined with systemic steroid therapy (with intubation for airway protection), the success rate may increase [14]. However, the use of intralesional injections may require prolonged intubation, a greater number of intubations and multiple injections [4,8,17]. Not surprisingly, intralesional steroid injection appears to be more beneficial in smaller, more focal lesions, although this has not been studied in AIH specifically [1].

Surgical therapy for AIH

Laser therapy

Lasers have been used to treat airway hemangiomas for more than 20 years [16]. They have the theoretical advantage of allowing focal tissue ablation despite a restricted working space within the airway. The published literature describes the use of a variety of lasers for airway hemangioma treatment, including CO_2, neodymium: yttrium-aluminum-garnet (Nd:YAG), and Nd:YAG via a potassium titanyl phosphate crystal (KTP). These lasers are typically used via an endoscopic approach, most often through direct laryngoscopy. Large, well-designed comparisons of these three lasers in the management of airway hemangioma are lacking. While some studies have found differences in outcome between the different types of laser, they are too small to reach reliable conclusions. The theoretical advantage of the KTP laser is the ability to administer it via a flexible fiber, potentially allowing for greater control and versatility than other lasers. It also has a shallow depth of penetration (approximately 2mm), thus allowing the surgeon to avoid collateral damage to deeper tissues. The CO_2 laser has a similarly shallow penetration with a slightly diffused beam and pulsed application [18].

Another possibility is the diode laser. This laser has been useful in larger studies of head and neck cutaneous hemangiomas [19], but only one study of 22 patients examined its use in the initial treatment of AIH [14]. In a majority of those patients, improvement in both symptoms and objective measurement of airway stenosis was achieved after diode laser therapy.

The use of endoscopic laser therapy in AIH has become commonplace, and this approach is often seen as a minimally invasive alternative to open excision. However, the use of lasers in the airway has the potential for significant complications. Laser therapy often requires more than one treatment session [14,20], with the patient being exposed to the risks of general anesthesia at each session. Each use of the laser also carries risks of burns, airway fires and complications of the endoscopic approach. In addition, and most importantly, laser use has been associated with an increased risk of subglottic stenosis (up to 25% of patients), particularly in patients with bilateral or circumferential lesions and in patients requiring multiple treatments [4,15,16]. In such cases, we suspect that the larger area of laser-associated injury may lead to greater scarring and stenosis. This risk is probably present for any type of laser, as all lasers function by delivering energy to create tissue damage. Finally, in patients who later require open excision of their lesion, prior laser use may make dissection more challenging [21], possibly due to scarring after laser-induced tissue injury.

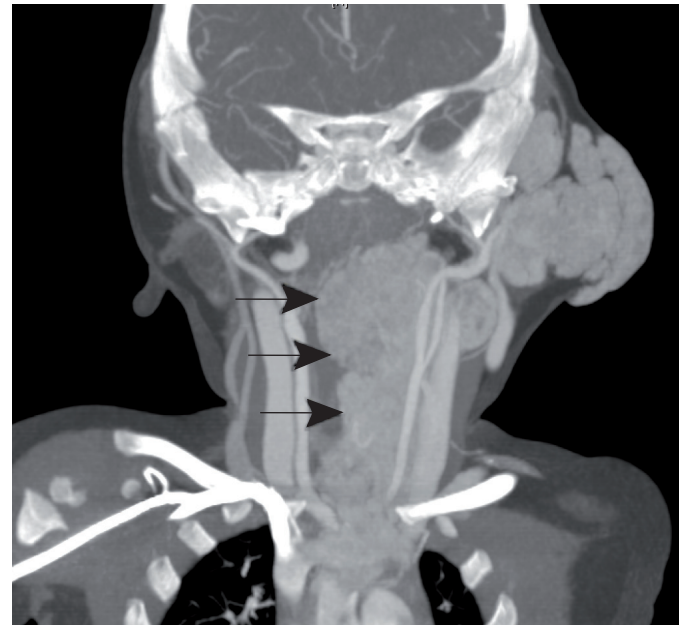

Figure 3. Coronal computed tomography image demonstrating the enormous extent infantile hemangiomas can reach. Arrows indicate large component in the neck that includes airway infantile hemangiomas.

Despite the lack of data on its comparative effectiveness, and despite its potential complications, the laser is a viable option for treatment of AIH, particularly for small, unilateral lesions. As with any invasive airway procedure, we would recommend that the surgeon be very comfortable with the pediatric airway before proceeding.

Open excision

At some centers, open excision is the preferred treatment method for AIH [22,23]. Access to the lesion is typically achieved with an anterior airway incision, either through the cricoid cartilage or via a laryngofissure that divides the entire anterior wall of the larynx. Dissection usually proceeds in a submucosal plane [22] in order to avoid stripping mucosa and promoting associated scarring. Depending on the status of the airway after excision, some surgeons prefer to insert a cartilage graft from the rib or another location into the split made in the cricoid cartilage in order to maintain airway patency by increasing subglottic airway circumference. Postoperatively, patients typically require several days of intubation if they do not already have a tracheostomy [4,22].

In published studies of open excision, the procedure appears to be generally effective, with more than 90% of patients categorized as treatment successes [22,23], although the definition of treatment success is usually not clearly defined. Furthermore, no studies have been published with long-term follow-up of these procedures.

Potential systems-level drawbacks of open excision include long operative times and the need for prolonged stays in the intensive care unit. For the individual patient, potential complications include subglottic stenosis, particularly in patients

who do not receive a cartilage graft and possibly in patients who have undergone previous laser procedures [21]. In addition to subglottic stenosis, other scar-related complications may occur, including anterior glottic webs at the laryngofissure site and granulomas [22,23]. These lesions may warrant further endoscopic procedures.

Conversely, open excision has several potential advantages over other therapies. Infants who undergo a single-stage excision and cartilage graft can often avoid tracheostomy [22,23], which may be a major quality-of-life benefit for both patients and their parents. In patients with pre-existing tracheostomy, open excision may also allow more rapid decannulation. When excision is successful, it also allows definitive treatment in a single procedure. Finally, it may be the best surgical option for patients with large, bilateral or circumferential lesions not amenable to laser therapy. However, this conclusion needs further testing; no direct comparisons to endoscopic treatment exist, and published outcomes do not control for the presenting stage of lesions.

Propranolol

The most recently described medical therapy for AIH is propranolol, a nonselective β-blocker. Propranolol's mechanism of action in hemangiomas is unknown, and its use is based on an incidental finding described in 2008 [24].

The literature on propranolol use for treating hemangiomas is still in its infancy, and studies of its use in AIH are limited to case reports and small series. In the case of cutaneous hemangiomas, the largest study to date included 32 patients, of whom 50% required no additional therapy beyond propranolol and 47% showed improvement with the drug but required additional therapies [25]. In several case reports of propranolol use with AIH, propranolol has led to dramatic reductions in lesion size and airway obstruction [26,27]. In some cases, the drug exhibited benefit in patients who had failed other therapies, including systemic and intralesional steroids, laser therapy and vincristine [28,29]. Typical doses consist of 2–3 mg/kg/day divided into three doses.

As with any drug therapy, adverse effects are possible. Of particular concern are cardiovascular side effects, including hypotension. Propranolol can also have airway, neurologic and gastrointestinal effects, including bronchospasm, lethargy, hypoglycemia and reflux [30], with the risk of hypoglycemia being higher in premature and very young infants. Accordingly, a careful history focusing on these systems must be performed prior to administration. At some centers, the history is supplemented with electrocardiography and a pediatric cardiology evaluation [25], although such protocols have not been systematically studied. Initiation of therapy should probably be done on an inpatient basis to allow monitoring of vital signs. Close follow-up is also essential, both to detect adverse effects and to titrate doses upwards as the child's weight increases.

Nevertheless, propranolol has significant potential strengths, particularly in allowing children with significant disease to avoid surgical procedures with their attendant risks as well as the potentially more debilitating adverse effects of therapies such as steroids [27]. Propranolol is a very new treatment that warrants further evaluation. It has yet to be compared with more traditional therapies for AIH, and no standard protocol exists for dosing, monitoring or treatment duration. The combination of propranolol and steroids may also warrant further study. However, initial reports are very encouraging, and it seems likely that this drug will become a mainstay in the treatment armamentarium.

Expert commentary

Airway IH are uncommon and, accordingly, large studies evaluating diagnostic, staging and therapeutic strategies are not yet available. In the context of this lack of evidence on which to base management decisions, priority belongs to accurate diagnosis, careful assessment of disease burden and airway risk, and the development of a therapeutic regimen that is as rational as possible. Diagnosis depends on direct airway assessment using direct laryngoscopy and rigid bronchoscopy. Appropriate imaging may also be useful to assess total lesion volume and to determine the need for systemic therapy, although the use of imaging in AIH is another area requiring further study. Until a broadly accepted staging system and evidence-based diagnostic and therapeutic algorithms are available, readers must develop their own systematic approach to these potentially life-threatening lesions. This article is intended to assist them in doing so. Nevertheless, we should state that our general preference is to use medical therapy first, followed by surgical therapy as needed.

Five-year view

The management of AIH has evolved dramatically over the past two to three decades. Over the coming 5 years, we expect that this field will continue to evolve rapidly. We propose seven potential themes that are likely to be at the forefront of laboratory and clinical investigation.

First, the evaluation and diagnosis of AIH warrants investigation. While staging systems have been proposed [9], most authors have not yet begun to use a standardized system to allow broader comparisons between patients and studies. Systems to assess disease burden will ideally include symptoms, and clinical findings including rigid endoscopy and imaging data, since a combination of subjective and objective measures is necessary to measure burden completely. We show here one proposed approach to the systematic evaluation and management of AIH (Figure 4). It is important to point out that while imaging is a part of the algorithm shown here, its utility needs further study. Computed tomographic imaging is a viable option because it is quick and can be performed on unsedated infants without intubation. However, it increases the cost of care, and the cost–benefit balance of such imaging in AIH has not yet been elucidated [9].

Second, the evaluation of treatment outcomes has much room to grow. There is currently no standardized method for quantifying and comparing treatment outcomes in IH at any location, preventing thorough evaluations and comparisons of

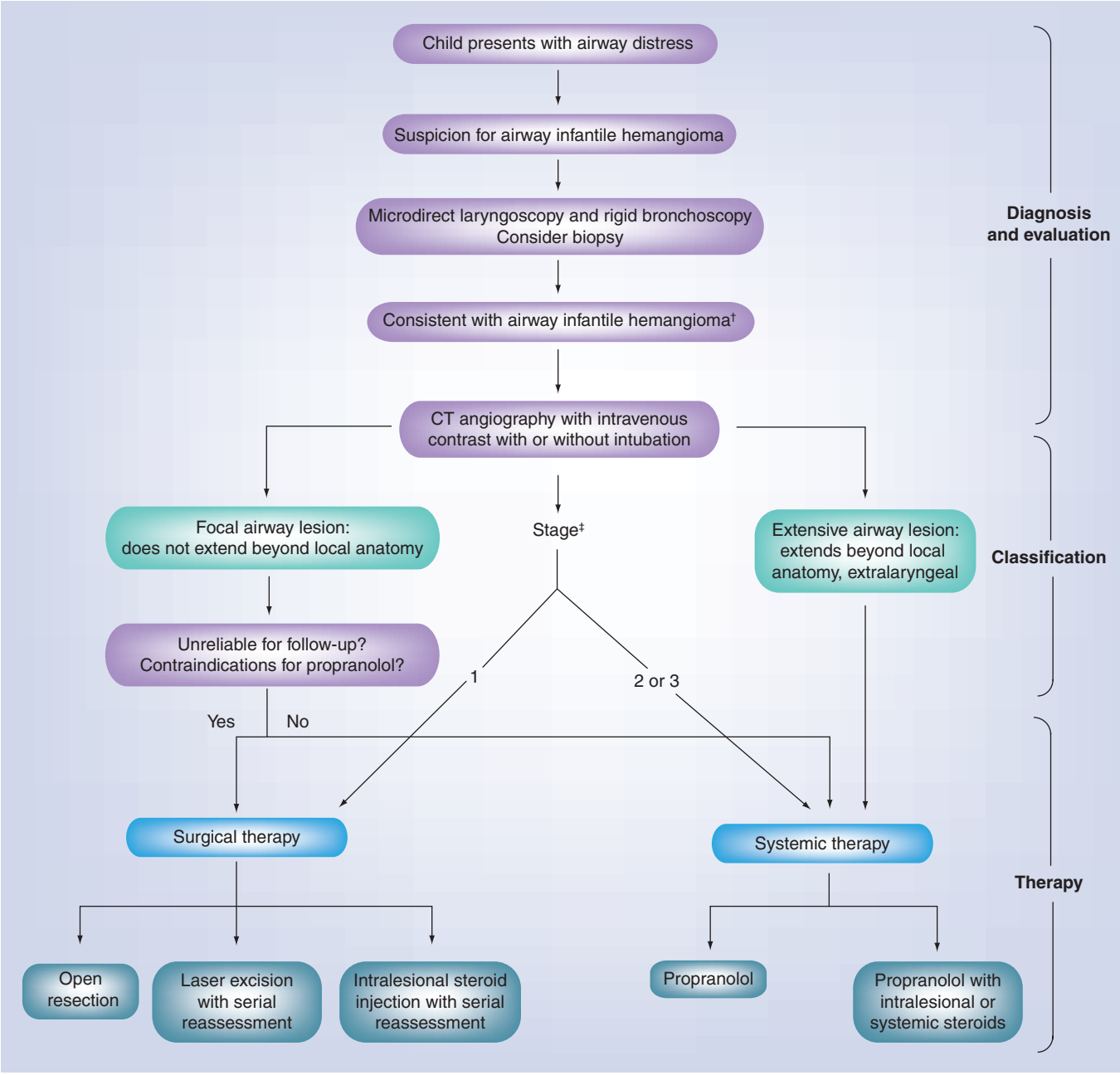

Figure 4. Example of a systematic airway infantile hemangioma evaluation and treatment algorithm. Both imaging and direct visualization of the lesion (with direct laryngoscopy and rigid bronchoscopy) are important in determining appropriate therapy.
†All treatment failures should consider biopsy to confirm diagnosis of airway infantile hemangioma.
‡Stage designations are based on [30].

existing and new therapies. This need will become more pressing as cost–effectiveness increasingly becomes the driving force behind treatment selection. Change in AIH stage is one possible measure [9], but no staging system is now commonly used or has been validated as an outcomes measure. Given the rarity of AIH, generation and validation of an outcomes measure will occur most effectively through multicenter collaborations that are currently in development.

A third theme is that propranolol warrants further study. To date, no trials have been published evaluating this therapy compared with controls or with other, more traditional treatments. There has also been no standardization of dose and treatment regimens. Furthermore, the very mechanism by which propranolol exerts its effect is unknown, although it appears to be effective in both the proliferative and involutional phases of AIH evolution. It may act via vasoconstriction, inhibition of pro-angiogenic or vasculogenic factors, or induction of capillary endothelial cell apoptosis [31]. If this mechanism is understood, it may be possible to design drugs that act in the same manner but more selectively, without some of the side effects

of propranolol that require close monitoring and follow up. It will also be useful to study the effectiveness of combined propranolol and steroid therapy.

The next trend we anticipate is the use of targeted biologic or molecular agents, including antiangiogenic agents. One agent commonly used in cancer treatment is bevacizumab, a recombinant monoclonal antibody against VEGF, a key factor in blood vessel growth. It appears that high-affinity receptors typically sequester VEGF. However, in hemangiomas, these receptors are underexpressed, allowing VEGF to bind to the VEGF receptor (VEGFR)2, another receptor that promotes endothelial cell proliferation and migration, possibly contributing to lesion growth [32]. VEGF also appears to promote IH endothelial cell proliferation *in vitro*. Accordingly, it might be expected that bevacizumab would inhibit VEGF activity and thus inhibit hemangioma growth. This idea is supported by a report of incidental improvement in a hepatic hemangioma when the drug was administered for another reason [33], and by intravitreal injection of the drug to treat retinal hemangiomas [34]. However, a valid concern is that this drug will suppress all vessel growth in infants, in whom vessel growth is essential for normal development. While discussing VEGF, it is worth mentioning that steroids may exert part of their effect on AIH by inhibiting VEGF-A expression [35], although they of course have many other effects that are not specific to AIH.

In conjunction with the expanding use of such agents, we anticipate a better understanding of the basic biology of AIH. While AIH were previously thought to be related to abnormal angiogenesis (the abnormal growth of blood vessels from preexisting vessels), they are now thought to also show abnormal vasculogenesis, which involves new vessel formation by progenitor or stem cells [36]. As this understanding improves, AIH-specific VEGF inhibitors that are safer to use in developing infants may become available.

Another possible theme that may become prominent over the next few years is the use of individualized therapy. *In vitro* culture of tumor cells currently allows detailed analysis of individual patients' tumors, including drug sensitivity and resistance testing in some cancers. This idea can theoretically be extended to other tumor-like diseases such as hemangioma. It is possible to grow cells from a specific patient's lesion either *in vitro* [37,38] or in an animal model such as a mouse, and it should be possible to test various therapies in order to determine which might be most effective. This idea has great potential for benefit, but it also has drawbacks; for example, the time required to grow cells in a laboratory setting and to test various therapies might not be compatible with the relative urgency of airway narrowing due to hemangioma [37]. Furthermore, as with many diseases, it is unclear whether treatment results *in vitro* or in the mouse translate directly to the human. Nevertheless, we are eager to see how this possibility unfolds.

Finally, surgical therapies continue to evolve. Endoscopic laser therapy is appealing owing to its relative safety, speed and lack of external invasion into the airway. However, as discussed earlier, laser treatment of larger lesions carries a significant risk of subglottic stenosis. As laser devices improve, it may be easier to cool the surrounding tissue during treatment, either through pulsed coolant or through miniscule pauses in the laser emission itself [18]. It may also be easier to prevent subglottic stenosis as endoscopic techniques for treatment of airway stenosis improve. At our center, we perform endoscopic posterior cricoid split operations with rib cartilage graft for subglottic stenosis [39]; it may be possible to perform this procedure preemptively in patients requiring extensive laser treatment. Alternatively, it may be safer to treat these patients with this endoscopic procedure should they develop subglottic stenosis.

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Key issues

- Infantile hemangiomas are vascular tumors of infancy that occur most commonly in the head and neck and can cause life-threatening airway compromise.
- Airway infantile hemangiomas commonly occur in the subglottis but can appear anywhere in the airway. Suspicion for airway lesions should be high in patients with 'beard' distribution cutaneous lesions.
- Treatment options include interferon, steroids, endoscopic laser therapy, open excision and propranolol.
- No large trials exist for any of these therapies, but steroids, laser therapy and open excision are commonly used today. Steroids alone are not often effective and can cause potentially severe morbidities.
- Laser therapy is particularly useful for small, unilateral lesions. In larger bilateral or circumferential lesions, laser therapy can cause subglottic stenosis.
- Open excision is a viable option in patients with larger lesions and in order to avoid tracheostomy, but it requires more infrastructure than other modalities.
- Propranolol is a very promising new medical therapy, but its mechanism of action is unknown and published data are limited to case reports.
- Possible future directions of treatment include targeted molecular therapies and individualized therapy.

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