Interventional Treatment Options in Children with Extracranial Vascular Malformations

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Abstract

Extracranial vascular malformations vary greatly and belong to the complex field of orphan diseases and can involve all segments of the vascular tree: arteries, capillaries, and veins, and similarly the lymphatic system. The classification according to the International Society for the Study of Vascular Anomalies (ISSVA) represents an important guidance for selecting appropriate therapy. Although many of the principles of endovascular treatment, including image-guided sclerotherapy and embolization, are similar in adult and pediatric practice, there are some distinct differences regarding the treatment of vascular malformations of children. Thus, it is crucial to involve longer-term plan about managing these chronic diseases and their impact on a growing child. This review provides a detailed overview over the clinical presentation of venous, lymphatic, and arteriovenous malformations in children and emphasizes the specifics of their interventional treatment options, including distinct pediatric dose limitations and procedure-related side effects.

Keywords
► vascular malformation
► pediatric intervention
► endovascular treatment

Zusammenfassung

Malformationen bei Kindern. Von entscheidender Bedeutung ist, die Behandlung dieser chronischen Erkrankungen und ihre Auswirkungen auf das heranwachsende Kind längerfristig zu betrachten. Diese Übersicht gibt einen detaillierten Überblick über die klinische Präsentation venöser, lymphatischer und arteriovenöser Malformationen bei Kindern und hebt die Besonderheiten der interventionellen Behandlungsoptionen hervor, einschließlich der spezifischen pädiatrischen Dosisbegrenzungen und thera- pieassoziierter Nebenwirkungen.

**Introduction**

Vascular malformations are part of the vascular anomalies spectrum, besides the second major entity of vascular tumors. Both main groups represent disease patterns frequently becoming apparent in childhood. While infantile hemangiomas, representing the most common group of vascular tumors, regularly demonstrate characteristic clinical features and a dedicated course during the first year of life, vascular malformations, according to their definition, are present from birth and may become clinically obvious during childhood or adolescence. Consequently, a majority of patients suffering from extracranial vascular anomalies become symptomatic before adulthood and their clinical course may already be anticipated at this time. Further difficulties may arise, such as to determine the most appropriate time point for therapy or balancing the patient’s age against potential developmental impairment. While the therapeutic spectrum for the treatment of infantile hemangiomas focuses on watch-and-wait or propranolol, followed by the application of different laser therapies or conventional surgery for residual hemangioma tissue, image-guided sclerotherapy or embolization are frequently the most appropriate therapy for different kinds of vascular malformations in children. Specific genetic analyses are becoming increasingly important to look for underlying mutations while identifying potential syndromic diseases in patients with complex lesions. Molecular-targeted therapy might become a possible therapeutic option in the future and is increasingly being applied in an off-label mode after identification of specific targets.

Although the major principles of interventional treatment are similar in the adult and pediatric setting, there are some important differences in the approach for children, such as considering the impact of this chronic disease on a growing patient. Irrespective of the localization of the malformation, size reduction via interventional treatment in the form of sclerotherapy or embolization is usually aimed at reducing lesion extent, either as a sole treatment or prior to elective surgery additionally reducing the risk of perioperative complications, such as bleeding. In case of extensive vascular malformations, repeated procedures may be required; thus, this fact has to be conveyed to the children and their families in a patient-centered and positive manner. Moreover, as vascular malformations rarely can be cured entirely, treatment goals have to be defined together with the child and family, to avoid misunderstanding and disappointment in cases when parts of the lesion persist even after multiple treatments. Inter- and multidisciplinary treatment strategies in specialized vascular anomalies centers proved to achieve the best outcome results, where providing comprehensive care is in line with the current state of knowledge and experience. As interventional radiology offers minimally invasive image-guided interventions besides a high diagnostic expertise, interventional radiologists can act as a coordinator within this interdisciplinary framework. In cooperation with the other clinical disciplines involved, as pediatrics, pediatric surgery, visceral surgery, ENT, plastic surgery, urology, and hemostaseology, an optimal and comprehensive treatment concept can be designed, in which each specialist contributes its relevant expertise. This review aims to highlight the detailed clinical presentation of the different subtypes of venous (VM), lymphatic (LM), and arteriovenous malformations (AVM), as well as the corresponding interventional treatment options including radiation dose limitations and procedure-related side effects while considering the specificities related to pediatric patients.

**Interventional Treatment Options**

As most vascular malformations involve multiple anatomic compartments, these cases are not suitable for superficial treatment or surgical resection alone. Regularly, interventional procedures consist as the first-choice therapy for children, particularly due to the adequate risk–benefit ratio, or they are combined with surgical resection. Although the malformation is not removed by the image-guided intervention, these options may lead to size reduction, functional improvement, and decreasing pain.

Interventional treatment options include sclerotherapy, endoluminal ablation therapy, and embolization; an overview is provided in Table 1.

Sclerotherapy is used for treating symptomatic slow-flow vascular malformations, especially VMs and macrocystic LMs. The sclerosing agents introduced by direct puncture initially cause inflammation of the vessel wall, followed by fibrosis of the lesion.

Endoluminal ablation procedures are mainly used in the management of embryonic dysplastic veins, such as the marginal vein (MV). In the case of connections to the draining deep vein system, their occlusion is essential for the prevention of thromboembolic complications.
Emboli occur mostly sporadically. They appear as common VMs presenting with focal, multifocal, or diffuse manifestations, as well as part of syndromic disorders (e.g., blue rubber bleb nevus [Bean] syndrome). Errors during venous embryogenesis result in dilated and dysfunctional thin-walled veins and venules with scant smooth muscle cells, which can involve any organ and multiple tissue types resulting in a range of morphologies, from well-defined, spongiform lesions to complex tangles of dysplastic veins (see Fig. 1). Clinically, VMs manifest as soft, nonpulsatile, and compressible lesions that usually show a bluish/purplish discoloration in case of superficial lesions. VMs can increase in volume due to increased hydrostatic pressure, extremes of temperature, or Valsalva. Their growth can be stimulated following trauma or partial resection as well as during hormonal changes at puberty or pregnancy. Symptoms of VMs include pain, swelling, disfigurement, functional impairments, and localized intravascular coagulation (LIC) with raised fibrin degradation products, which may cause recurrent thrombosis and thrombophlebitis. The latter, a unique chronic consumptive coagulopathy, occurs particularly in

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**Table 1** Overview of interventional treatment options in children

<table>
<thead>
<tr>
<th>Interventional treatment option</th>
<th>Short description</th>
<th>Indication</th>
<th>Agents/Probes</th>
<th>Adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sclerotherapy</strong></td>
<td>Vessel sclerosis by means of a sclerosing agent, insertion via direct puncture</td>
<td>VMs, macrocystic LMs</td>
<td>Ethanol (VM) Gelified ethanol (VM) Polidocanol (VM) OK-432 (LM) Doxycycline (LM) Bleomycin (LM)</td>
<td>- Local side effects such as necrosis and irreversible nerve injury, systemic complications such as central embolisms (ethanol as most aggressive agent with up to 20% major complications)</td>
</tr>
<tr>
<td><strong>Endoluminal ablation</strong></td>
<td>Endoluminal vessel sclerosis by means of laser or hyperthermia</td>
<td>Marginal veins</td>
<td>Laser/radiofrequency probes</td>
<td></td>
</tr>
<tr>
<td><strong>Embolization</strong></td>
<td>Occluding vessels by means of embolization materials (embolization agents, plugs, coils), in most cases endoluminally via inserted angiographic catheters</td>
<td>AVMs, AVFs</td>
<td>Ethanol (AVM) N-butyl-2-cyanoacrylate (AVM) Ethylene-vinyl-alcohol-copolymer (AVM) Plugs/coils (AVF)</td>
<td>- Risk of accidental nontarget embolization via the venous outflow (due to high blood flow) - Biological aggressiveness of the underlying disease with risk of rapid recurrence after incomplete embolization</td>
</tr>
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</table>

Abbreviations: AVM, arteriovenous malformation; AVF, arteriovenous fistula; LM, lymphatic malformation; VM, venous malformation.

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**Legend for Figure 1**

A) MR images of an extensive venous malformation. Coronal view demonstrates T2 hyperintense dysplastic venous cavities, beginning in the subcutaneous fat (arrow) infiltrating the masseter muscle and deeper tissues. B) Transverse images reveal infiltration of all tissue layers extending into the paratracheal structures, imposing a high risk for tracheal stenosis (asterisk) or occlusion in case of volume increase of the lesion; lower left image shows CT-guided puncture of paratracheal malformation for sclerotherapy. C) Dynamic MR angiography reveals only late filling of the malformation (arrow), corresponding to the slow-flow situation. D) Fluoroscopy following percutaneous puncture and contrast injection reveals communicating dysplastic venous channels, infiltration of all tissue layers of the face and neck.

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larger VMs, while this ongoing consumption of clotting factors due to stasis in the lesion may result in severe systemic coagulopathy accompanied by low factor XIII, low fibrinogen levels, and increased D-dimers in extensive cases. These complications may significantly limit daily activities and the negative impact on a child’s quality of life consecutively contributes to a family’s decision to pursue rather aggressive therapeutic strategies. In addition, LIC increases the children’s risk for intraläsional thrombosis as well as the peri-interventional risk for hemorrhage.\textsuperscript{27–29} VMs with LIC show all components of the Virchow’s triad including abnormality of the vascular wall, stasis of blood flow, and activation of the coagulation cascade.\textsuperscript{30} Here, a multidisciplinary approach and experienced hemostaseological management including extended coagulation function indexes, such as prothrombin time, thrombin time, activated partial thromboplastin time, international normalized ratio, fibrinogen, antithrombin, platelets, and D-dimers, as primary indicators of LIC are crucial.\textsuperscript{31} Severe thrombogenic coagopathies in children especially with large vascular malformations can be improved by anticoagulation.\textsuperscript{26}

Similar to the therapeutic strategies in adults, treatment of pediatric VMs includes conservative (anticoagulation, compression garments), interventional (sclerotherapy), and surgical options. Depending on the clinical appearance of the lesion, conservative treatment can suffice, exemplarily reassuring that small pain-free malformations do not progress into more aggressive VMs. In case of mass effect or venous congestion, well-tailored compression garments may relieve symptoms in a simple and noninvasive manner.\textsuperscript{32} If their wearing is accepted by the young patients, these are an effective tool, particularly in dependent lesions as well as in VMs presenting aggravated in activity.

In general, sclerotherapy is considered as the first-line intervention for VMs in both children and adults. Several pediatric studies could show that it is effective in shrinking small lesions while controlling symptoms in larger lesions.\textsuperscript{33–36} Sclerotherapy has been proven to close and scar the dysfunctional veins and venules, and consequently to reduce venous congestion, mass effect, and thrombosis.\textsuperscript{37} An important aspect in case of pediatric patients is an intrarticular lesion extension, presented frequently around the knee, as this may lead to recurrent hemarthroses with consecutive potential to cause destructive arthropathy.\textsuperscript{38} Preventing this severe complication indicates early intervention even in asymptomatic joints of young children. While the choice of the sclerosing agent is rarely different between adults and children, it is essential to keep in mind that there are severe potential side effects and specific weight-dependent dose limitations.

For several years, ethanol has been the most frequently used sclerosant, but has recently lost its popularity due to high complication rates including nerve injury and skin necrosis, as well as dose limitations by the risk of respiratory depression, rhabdomyolysis, cardiac arrhythmia, or sudden death. These local and systemic side effects are described already using low doses,\textsuperscript{39,40} which consecutively should be weighed against the high effectiveness of ethanol due to direct vessel wall necrosis and disruption of erythrocytes, with subsequent thrombosis and fibrosis of the intima.\textsuperscript{41}

Sodium tetradecyl sulfate (STS) is a commonly used agent with maximum effectivity owing to the detergent properties including its interference with cell surface lipids. STS is characterized by high endothelium damage while producing low thrombus formation with the result of fibrosis and consecutive shrinking of the lesion.\textsuperscript{37} Because of hemoglobinuria, there may be observed oliguria and urine discoloration within a few hours after STS sclerotherapy in particular after the use of relatively high amounts of the sclerosant.\textsuperscript{42} To avoid the risk of renal insufficiency, peri-interventional strategies as bladder catheterization and intravenous hydration have been proposed without being established as standard procedures. Although renal injury may mostly be temporary, it is advisable to remain within certain dose limits. Additionally, the amount of administered STS should be adjusted regarding the morphological characteristics of the lesion as well as the surrounding structures. Especially in restricted or anatomically sensitive areas (e.g., at distal extremities or the face), STS potentially causes relevant side effects as swelling, nerve injury, skin ulceration, or deep vein thrombosis.\textsuperscript{43} In children, a maximum (STS 3%) dose per endovascular treatment of 0.5 mL/kg can be assumed, up to a maximum of approximately 20 mL.\textsuperscript{44} The most frequent use of STS as foam is characterized by wide-ranging variations in its composition including the admixture of air, ethiodized oil, contrast medium, or albumin solution. The resulting foamed sclerosant slowly fills the dysplastic vessels while improving wall contact for efficient endothelial damage. Thus, pediatric patients benefit from an increased STS volume for the same agent dose.\textsuperscript{45}

Polidocanol, a synthetic long-chain fatty alcohol applied as foam, is characterized by slightly less treatment efficiency with a correspondingly lower side effect profile.\textsuperscript{46} Thus, polidocanol is a mild sclerotherapy option, but may show similarly good treatment results after repeated sessions.\textsuperscript{47,48}

Bleomycin, a cytostatic agent belonging to the class of antibiotics, differs in its underlying sclerosing mechanism from the previously mentioned sclerosants. As dismantling the solid stroma of vascular structures,\textsuperscript{49} it seems to be most efficient in comparatively spongiform VMs providing large stromal components. Bleomycin may not show neurotoxic effects; thus, it is reliably used near nerve structures. Additionally, postinterventional swelling or skin complications may be less common compared with other agents. Bleomycin can be admixed with ethiodized oil, albumin, or gelatin sponge slurry, to decrease the wash-out rate of the sclerosant from the lesion but potentially augmenting its efficiency.\textsuperscript{49} In case of resistance to prior invasive treatment, the combination of injected bleomycin with reversible electroporation may improve therapy outcome.\textsuperscript{20}

In case of relatively solid lesions presenting resistive to previous sclerotherapy, the evidence increases that percutaneous cryoablation may be a further feasible and safe treatment alternative.\textsuperscript{51–53}

MVIs are a special type of tubular VMs caused by defective development during the later stage of embryogenesis while
the vein trunk is already formed. Clinically, chronic venous insufficiency may occur due to a unique condition of avalvulosis. Additionally, MVs increase the risk for venous thromboembolism owing to the structural defect with a lack of smooth muscle cells to form the media properly as a truncular VM infrequently resulting in fatal pulmonary embolism. Together with LM, MV is one of two clinically most important congenital vascular malformation components among Klippel-Trenaunay syndrome. Beyond lateral MV excision, interventional treatment may present as alternative: Radiofrequency ablation was shown effective as the treatment of the marginal venous system (see Fig. 2), while it should be treated early in life. MVs with large diameter, intraligamentous courses, and residual tributaries frequently require additional coil embolization and sclerotherapy.

The categorization of VMs according to the Puig classification plays a crucial role as it may potentially predict the treatment response based on appearance and venous drainage. Type I VMs present isolated without detectable drainage into surrounding veins, type II VMs drain into nondilated normal veins, and type III VMs reveal drainage into dilated and type IV VMs into dysplastic veins. In the last two categories, both the success of minimally invasive treatment decreases and sclerotherapy has to be monitored carefully owing to potential agent dislocation into draining veins and consecutive systemic thromboembolism. This can be managed by using coils and/or glue to internally obstruct the outflow tract or simply by extrinsically placing pressure over the outflow vessels.

**Lymphatic Malformations**

LMs, found in 0.1 to 2% of the population, consist of circumscribed dilated, thin-walled channels and spaces containing lymphatic fluid, but without apparent connection to the lymphatic system. These lesions can be present at birth or occur later in early childhood, classified as macrocystic (e.g., cyst size ≥ 2 cm), microcystic (e.g., cyst size < 2 cm), and mixed type. Of note, there is no clear consensus considering this categorization of macro- and microcystic LMs. They typically affect the cervicofacial and axillary areas; nevertheless, LMs can potentially appear at any part of the body. Characterized by the appearance in young childhood, in general, they are timely treated prior to the transition to adult practice. They may grow fast and swell during concomitant infectious illnesses. LMs appear as a flesh-colored soft mass as well as blue colored in case of intralesional hemorrhage or intermittent infections. The latter is particularly frequent if the lesion affects mucosa. Involvement of skin or mucosa is characterized by fine surface vesicles, commonly with punctate black or red markings due to admixture of blood. Functional impairment of adjacent structures can lead to pain and swelling, additionally disfiguration of affected areas including cellulitis may be presented frequently. Microcystic lesions can be accompanied by localized fat hypertrophy, which is crucial to recognize, as this may limit the amount of bulk reduction that can be realized. The latter mostly (and aggressively) affects the bones, while...
GLA is described as multifocal cystic lesions involving numerous organ systems as well as the bones. Further clinical presentations of generalized LMs include splenic and hepatic cysts as well as pleural effusions.

Indications for endovascular treatment of LMs are intermittent infections, intralesional hemorrhage, mass effect, or functional and aesthetic impairment. Percutaneous sclerotherapy of macrocystic lesions should be performed with the aim to drainage them to near-total dryness (see Fig. 3). For simple macrocystic LMs, one endovascular procedure may suffice, while complex LMs may require multiple treatment sessions. Usually, infants and young children will, of course, require general anesthesia (GA) for sclerotherapy, non-GA procedures can be desirable and adequate for older children. It has been descripted that GA in the first year of life may have long-term effects on a child’s development; this may highlight the approach to delay endovascular treatment of asymptomatic LMs. Sclerotherapy of challenging, extensive macrocysts (e.g., frequently seen in neonatal cervicofacial or in mesenteric lesions) can be performed in use of pigtail drains with multiple sideholes inserted during the first treatment, which allows serial procedures over subsequent days while the children are awake. A small part of LMs shrink spontaneously in the first months after birth; in these asymptomatic, young babies, delay of intervention can be adequate. In case of indications for treatment immediately after birth, the aim should be to shrink the LMs to enable the child to move head and feed to put on weight before elective surgery some months later. Even if the macrocystic components are often impressive, superficially visible findings, it has to be kept in mind that the deep components are responsible for causing functional impairment. Regarding the head and neck lesions, as the most common localization, the possibility of swelling after sclerotherapy has to be considered, potentially requiring protective intubation for a few days. However, this complication should be generally possible to avoid if the procedure is performed carefully and with consideration of distinct high-risk locations (e.g., the tongue and the pharynx). The latter can pose even more clinical challenges: due to mucosal involvement, the tongue surface may be very susceptible to infection, bleeding, as well as irritation during feeding. If deeper tissue layers are affected, the children present with macroglossia.

Sclerosing agents in LMs do not require to be foamed, as 360-degree wall contact is easy to achieve in collapsed macrocysts, compared with VMs. Doxycycline is one of the most chosen sclerosants, due to its good availability, the high safety profile, and the reliable data existing on doxycycline sclerotherapy outcomes. The dose limits of doxycycline depend more on the children’s size than on the volume of

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**Fig. 3** Percutaneous image-guided sclerotherapy of a cervicothoracic lymphatic malformation in a 3-year-old-child. (A) Coronal T2-weighted fat-saturated MR image reveals (arrow) fluid levels indicative of recent hemorrhage. (B) Axial T2-weighted MR images present macrocystic lesion type with septal thickening (arrow) involving the right cervicothoracic area. (C) Following contrast application, only septal structures reveal prominent enhancement, while central lymphatic spaces do not fill with gadolinium. (D–H) Fluoroscopy-guided imaging and drainage of macrocystic lesions before inserting the sclerosing agent. (I) Percutaneous needle assessment and sclerotherapy using fluoroscopy guidance.
fluid drained. The recently reported recommendations amount to approximately 100 to 200 mg doxycycline per endovascular treatment in infants, 300 to 500 mg in young children, and up to 1,200 mg in adolescents. Based on systemic doxycycline absorption, postinterventional metabolic acidosis, transient hypoglycemia, and hemolytic anemia have been reported in babies. In general, monitoring of blood glucose levels should be performed in pediatric patients up to the age of 1 year (until they begin to feed again). To avoid stinging during injection, macrocysts can be pretreated with a small amount of local anesthesia.

STS may represent as alternative while demonstrating comparable complication rates. Mainly reported as just as effective as doxycycline, inferior outcome results have also been described.

OK-432 or Picibanil, a lyophilized form of group A streptococcus pyogenes, which is incubated with benzylpenicillin, is rarely used as sclerosant for lymphatic lesions currently, due to lack of availability, although excellent long-term outcomes have been shown. OK-432 may mediate its effect by stimulating inflammatory response of the endothelium via intercellular adhesion molecule 1 (ICAM-1) expression. There are reported low minor-complication rates including postinterventional pyrexia and transient swelling, though the latter has led to intubation and subsequent tracheostomy described in one case of LM located at the tongue.

Dual-agent approaches can be used in LMs not responding sufficiently to simple doxycycline sclerotherapy: Prior to intralesional administration of a standard dose of doxycycline, ethanol or STS can be instilled into the cyst while leaving it to dwell for approximately 5 minutes before aspirating it. Thereby, the first agent denudes the endothelial lining of the cysts enabling the second sclerosant to be more effective.

Microcystic LMs are significantly more difficult to treat: In rather solid lesions, bleomycin may achieve the most sufficient bulk reduction. Thereby, it is important to instill the entire lesion with bleomycin, involving the solid components or stromal tissue, as it may be even more effective in these areas. Similar to VMs, bleomycin can be mixed with further agents to increase viscosity, dwell time, and, consecutively, efficiency. In general, bleomycin as cytotoxic drug should be avoided under the age of 1 as well as the maximum dose should be restricted consequently in older children (15,000 IU per endovascular treatment from infancy: and a lifetime dose of 2–3,000 IU per kg up to 80–100,000 IU). When instilled in lymphatic lesions, it is very unlikely that bleomycin is absorbed systemically, though it may be good clinical practice to avoid additional oxygen if not clinically requested, as it potentially increases the risk of pulmonary fibrosis. Furthermore, the use of adhesives should be avoided peri-interventional as well as the children should be informed not to scratch their skin for approximately 48 hours after treatment, as bleomycin is washed out of the dermal soft tissue and also to avoid hypopigmentation. Bleomycin can also induce stinging on injection, which can be reduced by prior mixing with a small dose of local anesthetic.

Surgical debulking of complex or large LMs can often result in the postoperative formation of seromas. As in many cases predictable, this should not be seen as a treatment complication. The interdisciplinary team members should be aware that these seromas can be managed by endovascular treatment as well; thus, sclerotherapy through the surgical drains can be conducted if necessary.

Sirolimus, an inhibitor of the mechanistic target of rapamycin (mTOR), is reported to be effective in treating some types of LMs, as these lesions are result of somatic or mosaic PIK3CA mutations. Up to date, evidence is lacking on adequate dose regimes, or on which type of lesion may respond appropriately. Once sirolimus is stopped, there are high recurrence rates; additionally, the drug-related side effects may be significant. Due to this, the use of sirolimus is limited to complex or extensive lesions, such as generalized LMs. Furthermore, molecular-targeted therapy strategies are emerging and promising; for example, there is first evidence, which proposes direct inhibition of PIK3CA as therapeutic option providing clinical benefit in patients with PIK3CA-related overgrowth spectrum.

**Arteriovenous Malformations**

AVMs represent less than one-third of all types of vascular malformations. As fast-flow lesions, they may occur sporadic...
or associated with syndromes (e.g., Parkes-Weber syndrome, hereditary hemorrhagic telangiectasia, or CM-AVM). While persisting since embryonic development, AVMs are the result of an atypical direct connection between arteries and veins without an interposed capillary bed (see Fig. 4). Characteristically, there is a low-resistance net-like nidus linked to multiple feeding arteries and draining veins, whereas the normally intermittent capillary bed is either entirely or partly lacking. Histologically identified by thick-walled arteries and arterialized thick-walled veins, AVMs are most frequently located in the head and neck region. On clinical examination, superficial malformations may present relatively compressible and are accompanied by warmth, a pink-red cutaneous stain, and a palpable bruit or thrill. Owing to the fast-flow shunting, there is no gradual pressure decrease from the arterial pressure to the lower pressure on the venous side. This may have consecutive hemodynamic effects resulting in local hypervascularity, peripheral ischemia, steal phenomenon, and increased venous pressure with possible clinical features such as pain, tissue overgrowth, hyperemia, bleeding, ulceration, and gangrene up to high-output cardiac failure.

According to the Schobinger classification, the natural history is composed of four distinct stages: quiescent, growing, symptomatic, and decompensating. As during childhood, the aforementioned symptoms are rarely observed in full or sever expression, children frequently do not have clinical problems initially (during lifetime AVMs tend to continually progress). Similar to AVMs in adults, treatment decisions may be extremely challenging: While it is reasonable to delay invasive therapy until the AVM presents symptomatically, waiting may result in a situation which is already accompanied by significantly more difficult treatment conditions. Some of the childhood AVMs may show episodes of rapid growth, typically around puberty. Though it is challenging to predict which lesions will present like this, it further complicates adequate therapy decisions. A significant and common long-term effect of an AVM located in direct proximity to a growth plate is caused by its impact on bone growth. In these lesions, treatment should be performed even if the young patients are asymptomatic. Of note, embolization of these high-flow lesions may also result in asymmetric or impeded growth, requiring subsequent orthopaedic correction. The approach regarding embolization of extracranial high-flow lesions in children is in general similar to the one in adults.

In use of ethanol as embolic agent in children, cautious dose limits should be preserved. Based on its efficacy in damaging the endothelial tissue with consecutive eradication of angiogenic growth factors production, it may be highly effective in treating high-flow lesions. Due to the potential aggressive character, maintaining a dose limit of 0.5 mL/kg per procedure is suggested.

The nonadherent ethylene vinyl alcohol copolymer (EVOH)-based liquid embolic agents show a low tendency to migrate beyond the target sites, in comparison to ethanol. Additionally, they result in low inflammatory reactions of the vessel wall, while remaining intravascular with decreased permanent reaction of the surrounding interstitial tissue. Consecutively, fewer complications were described compared with pure ethanol, while EVOH offers distinct formulations with different degrees of viscosity and radioopacity. The effectiveness is high when used properly. Nevertheless, these agents also may be used with caution: EVOH-based liquid embolic agents are typically suspended in dimethyl-sulfoxide (DMSO). On agent administration, DMSO diffuses out of the solution and into the blood circulation, thus allowing EVOH to polymerize. After injection, systemic DMSO is excreted via the lungs. There have been described some cases of DMSO toxicity, including life-threatening complications as hemolyisis, pulmonary edema, and renal failure after AVM embolization using EVOH, which may be dose related. Further complications reported after EVOH embolization are procedure-related embolic events, skin necrosis, or local infections, the third may potentially induce consecutive EVOH extrusion.

Application of interstitial bleomycin has also been proposed as a further alternative of treating symptomatic high-flow lesions, although the mechanism of action of bleomycin in this setting is not yet understood in detail.

**Conclusion**

Vascular malformations are among the most challenging vascular diseases, especially in the pediatric setting. Defining the right timing of therapy is challenging, as lesion behavior and progression may not be predicted with certainty. Minimally invasive interventional treatments represent an important part of the multimodal therapy concepts in children and there are multiple sclerosing and embolic agents, each with specific characteristics. In addition to the already complex treatment decisions, there are specific features in children having to be considered during the procedures, including dose limitations and potential side effects. Beyond these interventions, also conservative options, surgery, and new treatment approaches such as molecular-targeted therapies should complement each other, individually used while adapted to the child’s clinical presentation and malformation type. Surgical debulking after size reduction may improve functionality while reducing recurrence rates. Novel combined strategies of interventional treatment and supplemented targeted drugs may provide better therapy outcomes and patient satisfaction. All in all, a multidisciplinary concept in specialized pediatric centers for vascular anomalies should be aimed at, in which the cooperating disciplines present with wide-ranging experience in longer-term therapy concepts.

**Conflict of Interest**

The authors declare that they have no conflict of interest.

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