

Management of Lymphatic Malformations



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KEYWORDS

• Lymphatic malformation • Lymphatics • Lymphedema • Sclerotherapy • Bleomycin • Sirolimus
• Surgery • Management

KEY POINTS

- The recent 2025 International Society for the Study of Vascular Anomalies Updated Classification of Vascular Anomalies updated the diagnoses of lymphatic malformations.
- Imaging diagnosis is sensitive and specific to guarantee diagnostic certainty.
- The timing of diagnosis represents a fundamental milestone in treatment decisions.
- The anatomic location and extent of lesions impact treatment decisions.
- A multidisciplinary approach and multimodal treatment based on new treatment options, derived from genetic and pharmacologic development, have improved the quality of treatment outcomes.

DEFINITIONS

Lymphatic malformations (LMs) are defined as a slow-flow vascular malformation with lymphatic differentiation. It is a relatively uncommon congenital vascular anomaly^{1,2} and most lymphatic malformations are associated with somatic pathogenic variants in PIK3CA and more rarely in BRAF genes.

The literature describes this condition as benign hamartomatous lesion involving the skin and subcutaneous tissue or as benign cystic mass arising from abnormal development of lymphatic vessels.^{1–5} More than half of LMs (50%–75%) is clinically present at birth, but symptoms often become more evident during childhood. According to Zhou and colleagues, 80% to 90% of cases not noticeable at birth are diagnosed around the age of 2 years.⁶ Lymphatic malformations are most found in the cervicofacial region (75% of cases). Tongue, lips, oral mucosa and neck are mainly affected^{3,4,6}; other frequent location sites are axilla and mediastinum.^{2,5} LMs are histologically featured by cysts

with varied sizes, constituted by endothelial cells and filled with lymphatic fluid.²

CLASSIFICATION

The International Society for the Study of Vascular Anomalies (ISSVA) 2025 Classification primarily divides LMs in 3 groups of diseases: isolated LMs, complex LMs, and lymphedemas⁷ (**Fig. 1**). Isolated LMs include macrocystic, microcystic, mixed macromicrocystic LMs, and angiokeratoma. Complex types of LMs include complex lymphatic anomaly, divided into generalized lymphatic anomaly (GLA), kaposiform lymphangiomatosis (KLA), Gorham-Stout disease (GSD), isolated or syndromic (RASopathy) central conducting lymphatic anomaly (CCLA) and generalized lymphatic dysplasia (GLD). Lymphedemas are classified as primary (isolated or syndromic) and secondary.

Macrocystic lymphatic malformations are LMs with predominance of large and few cystic

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Abbreviations

BEST	Bleomycin electroscrotherapy
CCLA	central conducting lymphatic anomaly
DC	apparent diffusion coefficient
DWI	diffusion-weighted imaging
EXIT	ex utero intrapartum treatment
GLD	generalized lymphatic dysplasia
GSD	Gorham-Stout disease
ISSVA	International Society for the Study of Vascular Anomalies
KLA	kaposiform lymphangiomatosis
LM	lymphatic malformation
MRL	magnetic resonance lymphangiography

components, although microcystic LMs have predominance of small and multiple cystic components (Figs. 2 and 3). The distinction between macro and microcystic lesions is clinically important, as it can help predict responsiveness to sclerotherapy treatment and guide the choice of

- Isolated
 - LM
 - Macrocystic
 - Microcystic
 - Mixed Macro-microcystic
 - Angiokeratoma
- Complex
 - GLA
 - KLA
 - GSD
 - CCLA
 - Isolated
 - Syndromic (RASopathy)
 - GLD
- Lymphedemas
 - Primary
 - Isolated
 - Syndromic
 - Secondary

Fig. 1. ISSVA 2025 classification of lymphatic malformations.



Fig. 2. Clinical appearance of macrocystic LM.

therapeutic agent. However, there is no standardized size cutoff separating the 2 types, and many patients have mixed types of cysts within the same lesion, referred to as combined isolated micromacrocytic lymphatic malformation or mixed lesions.

Angiokeratoma (Fig. 4) is included in LM since there is a major lymphatic component. The lesion is characterized by capillary ectasia in the papillary dermis associated with variable epidermal hyperplasia and elongation of the rete ridges enclosing the vascular channels. Lesions present as asymptomatic blue-red hyperkeratotic papules or plaques anywhere on the skin. It is a morphologic diagnosis with several etiologies, both genomically and clinically.

Complex LM (CLA) encompasses a list of rare diseases of more severe clinical presentation, frequently diffuse and with systemic compromise. GLA is a rare multisystem congenital disease characterized by diffuse proliferation of lymphatic channels in osseous and extraosseous tissues. The pathogenesis includes somatic pathogenic variants in the RAS/PI3K/mTOR signaling pathway. Patients with GLA have bone and visceral involvement, but in contrast with Gorham-Stout disease, cortical bone is not affected.

KLA, although it has some overlap with generalized lymphatic anomaly, is a rare aggressive disease characterized microscopically by excessive, dilated, and abnormally formed lymphatic

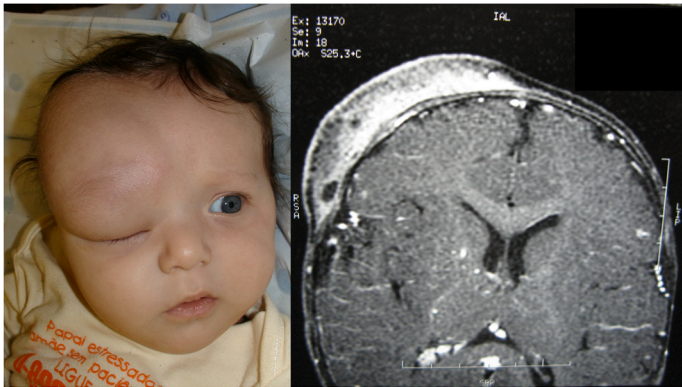


Fig. 3. Microcystic LM in the frontorbital area. Clinical and MRI appearance.

channels accompanied by scattered clusters of variably canalized, often hemosiderotic, spindled lymphatic endothelial cells. KLA usually presents during childhood, with respiratory symptoms, bleeding, and subcutaneous masses. Potential complications of KLA include thrombocytopenia and hemorrhage. Somatic pathogenic variants in *NRAS* have been identified in KLA.

In turn, GSD is a rare multisystem congenital disease that presents with aggressive osteolysis leading to loss of cortical bone in the context of a lymphatic anomaly; therefore, it is also known as *vanishing bone disease*.

CCLA is a serious condition that encompasses disorders caused by dysfunction of the thoracic

duct and/or cisterna chyli, with subsequent reflux and leakage of lymphatic fluid, most commonly into the lungs and/or abdomen. Pleural and pericardial effusions, ascites, and generalized edema are common and can result in organ dysfunction, protein loss, and infections. It can be isolated or syndromic, the former including the RASopathy group, in which the causative mutated genes are RAS-related genes.

Additionally, the rare GLD is caused by germline pathogenic variants in *PIEZO1*, *MDFIC*, and likely other genes. It is characterized by hydrops fetalis and generalized lymphatic dysplasia. Of note, Primary Generalized Lymphatic Anomaly, also known as Hennekam lymphangiectasia-lymphedema syndrome, is characterized by presence of intestinal and renal lymphangiectasia, dysmorphic facial appearance and cognitive deficiency. The facial features include hypertelorism, flat nasal bridge, epicanthic folds, small mouth, and small ears. The disease is associated with *CCBE1* gene genetic variants. This entity should not be confused with GLA from which it is entirely separate.

Finally, lymphedema is a diverse group of conditions that is also classified as lymphatic malformations and divided into primary or secondary. Primary lymphedema is usually related to hypoplasia of lymphatic vessels, leading to impairment of normal drainage of extracellular fluid. It can be an isolated disease or part of a specific syndrome. This category includes diseases such as primary hereditary lymphedema or primary lymphedema with myelodysplasia. Secondary lymphedema, on the other hand, is an acquired condition and can be caused by infection, radiation, malignancy, or surgery.

CLINICAL PRESENTATION

Clinically, LMs present as translucent lesions but may have reddish or yellowish appearance



Fig. 4. Angiokeratoma in the lower limb.



Fig. 5. Large LM in the left arm with active cellulitis and infection.

when mucosal involvement occurs. In addition, lymphatic cysts may contain blood or purulent secretion when accompanied by bleeding or infection⁶ (**Fig. 5**). When bleeding occurs within the lesion, the clinical presentation is characterized by a purplish appearance of the skin in microcystic lesions and a heterogeneous appearance of the contents in macrocystic lesions. Infected LMs can present with areas of soft tissue cellulitis, abscess formation, and associated septic conditions.

LMs most commonly occur in the head and neck region, representing 60% to 75% of cases, which may be related to the presence of a rich lymphatic system in these areas, followed by the axilla and mediastinum.^{6,8,9} Besides the physical disfigurement, impairment of lymphatic flow in LMs can cause severe dysfunction.^{2,4,5} The most affected areas are the lower two-thirds of the face (lips, buccal mucosa, tongue, and ears), and they frequently cause hypertrophy and deformities such as macroglossia, macrocheilia, and may be associated with mandibular hypertrophy.^{6,9,10} In the face, they can cause airway obstructions and significant anatomic distortions. Near skeletal

structures, they cause hypertrophy of these structures and can lead to malocclusions and joint disorders. Their dimension and progressive growth may cause compression on adjacent vital structures. Extensive lesions involving the floor of the mouth, oropharynx, and neck generally compromise the airways and may also cause compression of major vessels and nerves. Cervical malformations can compress the pharynx, mediastinum, and trachea, causing breathing difficulties.^{1,6} When present in thoracic or abdominal spaces, LM may lead to effusions and ascites, eventually leading to respiratory failure and other organ dysfunctions.¹

IMAGE DIAGNOSIS

Doppler ultrasound is typically the initial imaging modality in the evaluation of lymphatic vascular anomalies, largely due to its wide availability and ease of access. On B-mode imaging, it allows differentiation between macrocystic malformations—characterized by well-defined anechoic cystic spaces, usually larger than 1 to 2 cm, compressible and sometimes containing septations (**Fig. 6**)—and microcystic forms, which are composed of numerous small spaces, often ill-defined and with a more infiltrative pattern. In the latter, the typical cystic morphology may not be evident, and lesions may instead appear as areas of infiltrative soft tissue thickening, sometimes hyperechoic and with indistinct margins, reinforcing the need for correlation with the clinical context and other imaging modalities. Hypoechoic and heterogeneous lesions with a solid appearance, irregular contours, or poorly defined margins should raise suspicion for alternative diagnoses, including malignant neoplasms. Color and spectral Doppler further complement the evaluation by demonstrating low-flow characteristics or even absence of detectable flow in most lymphatic malformations. The identification of arterial or venous flow should raise suspicion of an associated vascular component, suggesting combined vascular anomalies.¹¹

MRI with intravenous contrast provides detailed lesion characterization by integrating detailed morphologic assessment with evaluation of enhancement patterns, and is currently considered the imaging modality of choice. T2-weighted sequences, particularly with fat suppression, highlight the fluid content and lesional characterization as high signal intensity and allow precise delineation of lesion extent and degree of infiltration across different planes. T1-weighted sequences, before and after contrast administration, enable assessment of progressive enhancement of lesion walls,



Fig. 6. Macrocystic LM in the supraclavicular area treated by bleomycin sclerotherapy. Intraoperative appearance of the cysts by ultrasound. 6 months postoperative appearance after a single session.

septa, and any associated solid components. Diffusion-weighted imaging (DWI) and apparent diffusion coefficient (ADC) maps may help differentiate simple fluid content from more complex components, such as hemorrhage or proteinaceous material. Additionally, isotropic 3D volumetric acquisitions allow multiplanar reconstructions and angiographic evaluation, improving assessment of relationships with adjacent structures and providing a robust anatomic basis for classification of these anomalies.¹²

Magnetic resonance lymphangiography (MRL) adds a functional dimension to the evaluation of these anomalies by enabling dynamic visualization of lymphatic flow. Through intranodal, interdigital, or targeted lymphatic injections combined with serial T1-weighted acquisitions, it becomes possible to track contrast progression throughout the lymphatic system. This approach allows identification of drainage patterns, reflux pathways, areas of stasis, and sites of leakage into serous cavities or soft tissues. As such, MRL refines the characterization of complex lymphatic malformations and enhances understanding of their communication with the central

lymphatic system, representing an important complementary tool to conventional imaging methods, particularly in the context of therapeutic planning.^{13,14}

MANAGEMENT OF LYMPHATIC MALFORMATIONS

Management of lymphatic malformations requires careful assessment of multiple factors, as shown in the flowchart. Historically, the first-line treatment of ML was surgical excision (**Fig. 7**). Although this treatment was reasonably effective or life saver, high recurrence and complications have encouraged the development of a less invasive approach. A clear shift in treatment has occurred with the inclusion of intralesional and systemic therapies, often in combined and multidisciplinary protocols. Currently, management involves clinical observation, pharmacologic therapy, minimally invasive procedures, laser techniques and surgical resection.

Expectant management is a valid strategy especially for patients with small, well-defined and asymptomatic lesions with minimal functional and aesthetic impairment.



Fig. 7. Preoperative, images and late postoperative appearance of a large LM treated by surgical resection with preservation of facial nerve function.

Sclerotherapy

During the last years, sclerotherapy has emerged as a promising alternative.^{5,15} The advantages over surgery are related to less complications that can occur from invasive procedures, such as damage to surrounding structures, including nerves and vessels, scarring, and recurrence due to incomplete excision. Sclerotherapy has become established as one of the main treatment options, especially for macrocystic or mixed lesions, in which aspiration of the contents and injection of sclerosing agents, such as bleomycin and doxycycline, has shown reliable results^{16,17} and are characterized by greater accessibility and distribution of the sclerosant agent into the cystic spaces.

In this context, the choice of sclerosant plays a critical role in treatment outcomes. Doxycycline, bleomycin and still ethanol are currently the most widely used agents, and offer balance between efficacy and safety. Bleomycin, in turn, has demonstrated particular utility in microcystic and mixed lymphatic malformations, as well as in lesions located near critical anatomic structures, given its relatively lower rate of inducing postprocedural inflammation and edema. In contrast, ethanol remains a highly potent sclerosant, particularly effective in well-defined cystic lesions. However, its use is limited by a higher risk of local complications, including skin necrosis, and is therefore generally reserved for selected cases. Overall, the literature supports an individualized approach

to sclerosant selection, taking into account lesion morphology, anatomic location, and patient-specific risk factors, within multidisciplinary treatment logic (see **Fig. 6**; **Fig. 8**).

Recent technologies to enhance the efficacy of sclerosing agents are the use of a foam mixture and electroporation techniques. With the association between polidocanol as a foaming agent, the use of a foam sclerosing agent can substantially enhance the therapeutic effects of bleomycin by slowing down the elution rate. Bleomycin electro-sclerotherapy (BEST) induces a temporary increase in cellular membrane permeability, whereby the intracellular concentration of Bleomycin increases. This may increase the efficacy of bleomycin, and initial promising results have been described in first studies of slow-flow malformations.^{18,19}

Pharmacologic Treatment

Knowledge about the pathogenic variants associated with somatic mutations in the PIK3CA gene has made it possible to block the mTOR metabolic pathway in controlling the disease and reducing the risk of progression. In this sense, mTOR pathway inhibitors, such as sirolimus, have brought about a major paradigm shift by helping to control lymphatic malformations.^{20–23}

Prenatal maternal administration of sirolimus has recently emerged as a promising but still experimental strategy for severe fetal lymphatic malformations, with early reports demonstrating



Fig. 8. Macrocystic LM in the submandibular area treated by bleomycin sclerotherapy. Preoperative appearance and result after 2 sessions of sclerotherapy.

transplacental drug transfer, reduction in lesion growth, and acceptable maternal–fetal safety profiles.^{24,25}

Surgery

More recently, advances in management for lymphatic malformations includes salvage procedures referred to as *ex utero intrapartum* treatment (EXIT), which is a strategy for treating fetuses with extensive cervical lymphatic anomalies and high risk of airway obstruction at birth. In this approach, when prenatal ultrasound demonstrates signs of airway compression or obstruction by lymphatic lesions, the uteroplacental circulation is maintained during the cesarean section while the neonatal airway is secured by orotracheal intubation, bronchoscopy or tracheostomy.²⁶

Surgical intervention remains an effective and recommended alternative. Surgical procedures are indicated for more localized lesions and specifically for the correction of associated deformities. Extensive resections, when indicated, must respect regional anatomy and anesthetic-surgical risks, otherwise significant postoperative morbidity or serious functional damage may occur. Among the most frequent surgical indications are microcystic lesions, isolated macrocystic lesions unresponsive to intralesional treatment, reduction of bone hypertrophy associated with LMs, and aesthetic and functional facial reconstructions.^{25–27}

New adjuvant intraoperative technologies applied in the surgical field increase safety of surgical excision of LM, avoiding complications.^{27,28}

- Vessel Sealing Energy Devices (Ultrasonic Harmonic Scalpel): vessel sealing properties promotes a trend for reduction in surgical

time, less postoperative leakage and less bleeding.^{27,29}

- Intraoperative neurophysiologic monitoring of nerve functions: monitoring motor and sensory nerve functions allows for anatomic and functional preservation and has established application in the approach to and resection of facial lesions for functional preservation of the facial nerve, and in lesions near vertebral nerve roots for motor and sensory preservation.³⁰
- Neuronavigation technologies, Virtual Surgical Planning, and customization of intraoperative guides for osteotomies and bone fixation methods have ensured better results in the treatment of associated skeletal deformities, mainly due to the degree of preoperative asymmetry that many of these patients present.²⁸

Lasers

Laser technologies have well-defined indications in the treatment of lymphatic malformations, mainly in the approach to intraoral lesions and those affecting the upper respiratory tract. Various types of lasers, such as Neodymium-doped Yttrium Aluminum Garnet (Nd-YAG), argon, and CO₂, which use water as a target chromophore, promote photocoagulation and tissue ablation of intraluminal components.^{31,32}

Multimodal Approach

Finally, advances in the understanding and diagnosis of vascular malformations are guiding treatment on multiple fronts.^{33–35} Various types of therapy, in different sequences and combinations, aim to reduce size and symptoms. An appropriate

rationale must, therefore, in addition to considering the timing of the diagnosis, encompass the clinical presentation and histologic aspect, anatomic location and extent of the lesion. Multimodal therapy aims to combine different treatment technologies with the best indications, based on outcomes (Figs. 9–11).

1. Onset of Diagnosis

a. Prenatal

- i. Consider oral sirolimus during pregnancy
- ii. Consider EXIT procedure during delivery

b. Early life

- i. Expectant
- ii. Oral sirolimus
- iii. Intralesional sclerotherapy
 1. Doxycycline
 2. Bleomycin

iv. Laser

c. Childhood

- i. Oral sirolimus
- ii. Intralesional sclerotherapy
 1. Doxycycline
 2. Bleomycin
- iii. BEST
- iv. Surgical Resection
- v. Laser

d. Adulthood

- i. Intralesional sclerotherapy

1. Bleomycin
2. Doxycycline

ii. BEST

iii. Surgical resection

iv. Oral sirolimus

2. Type of Malformation

a. Macrocystic

i. Intralesional sclerotherapy

1. Bleomycin
2. Doxycycline

ii. Oral sirolimus

b. Microcystic

i. Oral sirolimus

ii. Surgical resection

iii. Intralesional sclerotherapy

1. Bleomycin
2. Doxycycline

iv. BEST

c. Mixed

i. Intralesional sclerotherapy

1. Bleomycin
2. Doxycycline

ii. BEST

iii. Oral sirolimus

iv. Surgical Resection

d. Angiokeratoma

i. Surgical resection

e. Bone involvement

i. Surgical procedures



Fig. 9. Macrocystic LM in the submandibular and cervical areas. Multimodal treatment with bleomycin sclerotherapy followed by oral sirolimus. Preoperative appearance and result after 2 sessions of sclerotherapy.



Fig. 10. Microcystic LM in the tongue and oral cavity. Multimodal treatment with combination of oral sirolimus and bleomycin sclerotherapy. Preoperative appearance and result after 2 sessions of sclerotherapy during sirolimus therapy.

- 1. Epiphysiodesis
- 2. Debulking procedures
- ii. Oral sirolimus
- f. Complex (GLA, GSD, and KLA)
 - i. Oral sirolimus
- g. RASopathies
 - i. MEK inhibitors
- 3. Anatomic Location
 - a. Head and Neck
 - i. Intralesional sclerotherapy
 - 1. Bleomycin
 - 2. Doxycyclin
 - ii. Surgical resection
 - b. Airways
 - i. Intralesional sclerotherapy
 - 1. Bleomycin
 - ii. Laser
 - c. Thorax
 - i. Intralesional sclerotherapy
 - 1. Bleomycin
 - 2. Doxycyclin
 - ii. Oral sirolimus
 - iii. Lymphatic channel embolization (Major vessels)

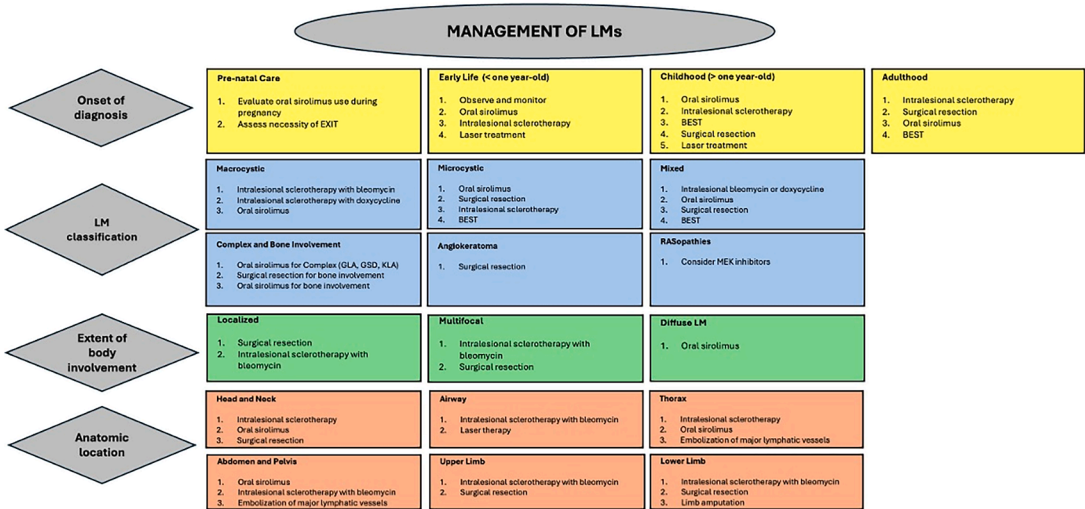


Fig. 11. Management algorithm for LMs stratified by clinical category.

- d. Abdomen and pelvis
 - i. Oral sirolimus
 - ii. Intralesional sclerotherapy
 1. Bleomycin
 - iii. Lymphatic channel embolization (major vessels)
- e. Upper limbs
 - i. Intralesional sclerotherapy
 1. Bleomycin
 - ii. Surgical resection
- f. Lower limbs
 - i. Intralesional sclerotherapy
 1. Bleomycin
 - ii. Surgical resection
 - iii. Debulking procedures
4. Body compromise
 - a. Localized
 - i. Surgical Resection
 - ii. Intralesional sclerotherapy
 1. Bleomycin
 - b. Multifocal
 - i. Intralesional sclerotherapy
 1. Bleomycin
 - ii. Surgical resection
 - c. Diffuse
 - i. Oral sirolimus

DISCUSSION

Although relatively rare, lymphatic malformations are relevant among vascular malformations due to the magnitude of the deformities caused and their locations, the associated diseases and complications, and the wide age range of involvement.

The important knowledge of the genetic components involved in the various presentations of lymphatic malformations has transformed the diagnosis not only in terms of its timing, but also by expanding the opportunities for systemic treatments, avoiding aggressive manipulations at early stages.

The current classification of lymphatic malformations was improved in the latest 2025 Classification of the International Society for the Study of Vascular Anomalies. The inclusion of the various types and subtypes, as well as isolated, complex diagnoses and those associated with systemic manifestations, allows the use of the classification by the general practitioner and the specialist.

The subdivision of isolated malformations, according to the dimensions of the lymphatic cysts, allowed for a more selective indication of intralesional and surgical approaches. Systemic diseases or those with diffuse anatomic involvement have found in pharmacologic therapy with mTOR

inhibitors such as sirolimus an efficient and safe treatment alternative.

Imaging diagnosis now establishes a reliable diagnostic certainty and can even be combined with image-guided treatment.

Ultrasound-guided sclerotherapy now represents a large part of treatments, through the safe and effective use of various agents.

Surgical treatment is then indicated more selectively, with greater precision of results. It is guaranteed as safe by the addition of surgical technologies for virtual planning, minimization of tissue damage, and protection of anatomic structures of functional relevance.

The existence of multiple efficient treatment alternatives allows for the individualized choice not only of the best method but also of the combination of therapies and the best temporal sequence of treatment, considering differentiated multidisciplinary expertise in the context of an appropriate temporal management throughout the lives of patients with lymphatic malformations.

SUMMARY

Current management of lymphatic malformations involves adopting current diagnostic methods that recognize the importance of malformation subtypes, the genetic variants involved, the potential benefits and risks of the technologies adopted, and a multidisciplinary and specific approach to anatomic locations and patient age range.

CLINICS CARE POINTS

- Currently, management involves clinical observation, pharmacological therapy, minimally invasive procedures, laser techniques and surgical resection.
- Sclerotherapy has become established as one of the main treatment options, especially for macrocystic or mixed lesions, in which aspiration of the contents and injection of sclerosing agents, such as bleomycin and doxycycline, has shown reliable results.
- mTOR pathway inhibitors, such as Sirolimus, have brought about a major paradigm shift by helping to control lymphatic malformations, even prenatally.
- Surgical procedures are indicated for more localized lesions and specifically for the correction of associated deformities. Surgery has also important role to warrant patency of airways.

DECLARATION OF AI AND AI-ASSISTED TECHNOLOGIES IN THE WRITING PROCESS

During the preparation of this work the authors used Gen AI. After using this tool/service, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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