Clinical Practice Guidelines for CLOVES Syndrome

CLOVES Syndrome Work Group

Vascular Anomalies Center

CLINICAL PRACTICE GUIDELINES FOR CLOVES SYNDROME

DISCLAIMER

The views expressed here are based on the available published data and the institutional experience of the Vascular Anomalies Center at Boston Children's Hospital.

This information: (1) Is not intended to substitute medical consultation with a qualified medical professional, (2) Does not constitute medical advice, (3) Does not represent the position of Boston Children's Hospital, and (4) Is based on the information known at the time of preparing this document and is subject to change.

Patient care and treatment should always be based on a clinician's independent medical judgment given the individual clinical circumstances. Every health-care professional making use of these recommendations is responsible for evaluating the appropriateness of applying them in the setting of any particular clinical situation.

CLINICAL PRACTICE GUIDELINES FOR CLOVES SYNDROME

OVERVIEW

CLOVES syndrome is a recently described non-inherited rare disorder. CLOVES designates **C**ongenital **L**ipomatous **O**vergrowth, **V**ascular malformations, **E**pidermal nevi, **S**coliosis/Skeletal/Spinal anomalies. Although common features are included in this acronym, several other findings exist in different body systems and organs.
The institutional knowledge and experience of our interdisciplinary team at the Vascular Anomalies Center (VAC) at Boston Children's Hospital were consolidated through managing and studying a large cohort of patients with CLOVES.
Standard appraisal of the quality of the evidence and recommendations was not performed. Nevertheless, the strength of evidence based on the Oxford Centre for Evidence-Based Medicine (CEBM) for the major categories (diagnosis, prognosis and therapy/prevention) in general are either level 4 or 5, which refers respectively to "case-series" and "expert opinion" without explicit critical appraisal.

GOALS

Here we list the clinical features of CLOVES syndrome and provide management guidelines, where appropriate, based on the best available evidence.
These guidelines aim to assist practitioners caring for patients with CLOVES syndrome patients and improve care by outlining some of the various clinical aspects of CLOVES syndrome and our current recommendations for management. The recommendations are organized by type and anatomical areas affected. Nevertheless, these guidelines are not intended to define a standard of care, nor should they be interpreted as prescription of an exclusive course of management.

GENERAL RECOMMENDATIONS

Referral

Given its rarity and complexity, patients with CLOVES syndrome should be referred to a specialized center with experience in managing complex overgrowth and vascular anomalies for confirmation of diagnosis, interdisciplinary assessment, delineation of clinical risks and complications, management and coordination of care.

Early Imaging Study (Early MRI)

CLOVES patients may benefit from an MRI of the chest, abdomen, pelvis and lower extremities performed in the neonatal or early infantile period or at the time of initial presentation. This help define deeper components of the syndrome that may require from intervention in early childhood (e.g. lymphatic and venous malformations, gastrointestinal and genitourinary involvement); as well as characterize overgrowth and extension into the retroperitoneum, peritoneum, superior and posterior mediastinum, pelvis, pleural spaces and paraspinal muscles, tethered spinal cord, neural tube defects).

If the study (herein referred to as "early MRI") requires general anesthesia, the scan can be delayed until the risk of anesthesia is reduced (i.e. > 6 months of age). Optimal timing of imaging best balances the risks of anesthesia with the information to be gained.

Genetics

CLOVES is diagnosed primarily on the basis of clinical and imaging findings. Discovery of the somatic mutation in *PIK3CA* gene in resected tissues from patients with CLOVES opens up the possibility of a medical therapy; PI3K and mTOR inhibitors are actively being investigated. Currently there are no commercially available genetic tests for detecting PIK3CA mutations. At the research level, droplet digital PCR can reliably detect the most common mutations. A positive test can confirm the mutation, whereas a negative test result cannot exclude the mutation. The presence or absence of the mutation does not define a patient as having CLOVES syndrome.

Nutritional Support

CLOVES patients with poor weight gain or failure to thrive may benefit from nutritional consultation and ongoing support. The presence of both fatty overgrowth in some areas and the appearance of malnourishment are frequent in CLOVES and not currently well understood. Many patients have improved weight gain in later childhood and some may improve after resection of large lipomatous masses.

Psychosocial Support

Comprehensive interdisciplinary management should address the psychological burden of the disease on the child and issues related to adaptation, coping, and distress. Management should aim at alleviating not only the physical issues, but also the psychological burden on the child and the family. Stress factors among caregivers should be identified so proper intervention or support can be provided. Social workers help families with coping with a diagnosis, mental health, parenting and behavioral concerns as well as identifying helpful resources. Psychosocial intervention can also be provided through community-based organizations or support groups.

VASCULAR ANOMALIES

Lymphatic Malformation

Lymphatic malformations (LM) in CLOVES vary in size from small skin vesicles of minor clinical significance to massive, deforming lesions, which are typically associated with fatty overgrowth. LM may macrocystic, microcystic or combined. The clinical consequences and treatment of these lesions vary widely. Small, superficial cutaneous vesicles are prone to leakage, bleeding, and increase the risk of infection. Larger lymphatic malformations, typically associated with overgrowth, are most commonly located in the chest and abdominal wall with variable extension into the abdominal and thoracic cavities. The morbidity of these lesions is related to mass effect (resulting in decreased range of motion and deformity) and infection.

Recommendations: Macrocystic lymphatic malformations can be treated with minimally-invasive techniques such as sclerotherapy. Large lymphatic malformations associated with overgrowth may benefit from surgical debulking. A combined approach with sclerotherapy and resection can be beneficial in selected patients.

When lymphatic malformations become infected, prompt evaluation and oral antibiotic treatment are necessary. Some patients may initially require intravenous antibiotics. Patients typically require a long course of at least 14 to 21 days of treatment. For recurrent infections, a prolonged course of prophylactic antibiotics should be considered. Infected lymphatic macrocysts may require drainage and sclerotherapy. Proper hygiene is imperative for cutaneous and mucosal lymphatic vesicles; they can be treated with sclerotherapy (including the use of bleomycin) or CO2 laser photovaporation.

For patients with significant complications from the lymphatic components of their disease, medical therapy with sirolimus has been used with promising early results. The use of sirolimus or other medical therapies is rapidly changing in CLOVES and other vascular anomalies and should be guided by an experienced hematologist/oncologist.

Venous Malformation (VM)(Phlebectasia)

Phlebectasia or dilatation of veins, in CLOVES syndrome is often seen in the upper and lower extremity and lateral truncal wall. These veins include orthotopic (normally located) or persistent embryonic veins. Involved orthotopic veins include the subclavian, axillary, innominate, intercostal, azygous, hemiazygous, short saphenous and jugular veins, as well as the superior and inferior vena cavae (IVC, SVC). Embryonic veins include the sciatic and marginal veins in the lower extremity and the lateral chest wall. Other anomalies, such as azygos continuation of the IVC, or persistent left SVC, may exist. Ectatic veins can be the source of blood clot formation and life-threatening pulmonary embolism (thromboembolism). In addition, patients may develop painful clots (thrombophlebitis).

Patients with an extensive VM may have altered blood tests due to stagnant or slowed blood flow and increased activation of the clotting cascade as an indicator of blood clot formation with VMs.

Recommendations: CLOVES patients may benefit from hematology evaluation including basic coagulopathy work up early in life and pre-procedurally.

- Thrombophlebitis can be treated with limb elevation, non-narcotic analgesics, and anti-inflammatory medications.
- Prior to invasive surgical procedures CLOVES patients may benefit from evaluation by an anesthesiologist and multidisciplinary optimization of physical status.
- CLOVES patients with dilated veins and increased risk of venous thrombosis may benefit from prophylactic anticoagulation during the perioperative period. A hematology consultation and a coagulation profile should be obtained before any procedure. Anticoagulation is often recommended both pre- and post-procedure to minimize the risk of blood clot formation and migration to the lungs. Placement of temporary IVC (or SVC) filters may also be considered.

- All patients should undergo preoperative imaging to assess the venous system. If an MRI has not been performed, proper imaging to evaluate the venous anatomy prior to any invasive intervention is strongly recommended.
Ultrasonography may demonstrate certain veins including subclavian, axillary, short saphenous and marginal veins in the lower extremity and the lateral truncal wall. Deeply seated veins (innominate, azygous, hemiazygous and sciatic veins as well as the superior and inferior vena cavae (IVC, SVC)) can be visualized by MRI or CT.
- Closure of the dilated veins may reduce the risk of thromboembolism, particularly prior to surgical procedures. We recommend closing specific dilated veins (lower limb and truncal marginal veins, axillary-subclavian, sciatic and short saphenous veins) early in life using minimally invasive techniques such as embolization and endovenous laser, by an experienced interventional radiologist.

Capillary Malformation (CM): See Skin

Arteriovenous Malformations

A subgroup of CLOVES patients develops a fast-flow vascular lesions or arteriovenous malformation (AVM). Most of these lesions are located in the paraspinal region and less frequently in the chest wall and extremities. Paraspinal AVM is associated with infiltrative fatty tissue in the posterior mediastinum that may extend into the spinal canal and cord, causing cord compression, venous hypertension and myelopathy.

Recommendations: Patients should be screened for these vascular lesions with an early MRI. If fast-flow anomalies or extension into the spinal canal are found, neurosurgical consultation and a dedicated spinal MRI, with sagittal and axial T2 and pre- and post-contrast T1 weighted sequences covering all potentially involved levels, are warranted. Patients who develop signs of spinal cord dysfunction (extremity weakness, urinary incontinence, constipation) should be promptly evaluated. Treatment may include spinal angiography, embolization and resection.
Depending on the degree of flow through a fast-flow lesion, cardiac function may be compromised. Evaluation by an anesthesiologist prior to a procedure may reveal the need for a cardiologist's assistance in perioperative management.

OVERGROWTH

Large lipomatous masses are most commonly located in the trunk and chest wall and can be associated with lymphatic and capillary malformations. These masses of variable size, are present at birth, and can be identified prenatally. Overgrowth can be unilateral or bilateral and may also extend into the abdominal wall, flank, gluteal and cervical areas as well as the extremities. Deeper extension may occur into the retroperitoneum, peritoneum, superior and posterior mediastinum, pelvis, pleural spaces and paraspinal muscles.

The clinical behavior of paraspinal-posterior mediastinal infiltrative tissue is distinct from the larger fatty masses. Paraspinal lesions can be hypervascular, aggressive and infiltrate into the epidural space and compromise the spinal cord and adjacent vessels.

Recommendations: Lipomatous overgrowth should be evaluated by a surgeon. Work up generally includes MRI of the affected areas. Surgical debulking of these lesions can improve mobility and quality of life. Removal of very large masses may also prevent growth disturbance of the underlying or nearby musculoskeletal structures (e.g. removal of a large chest wall mass may prevent rib cage deformity and resultant lung compression and restriction). When applicable, resection can include removal of cutaneous lymphatic vesicles, thereby reducing leaking and infection risk as well. Patients often require multiple staged operations. Lipomatous masses can regrow after resection, though this is difficult to predict for an individual patient.

Proper perioperative planning should be undertaken to prevent major complications such as thromboembolism. As mentioned above, initiation of perioperative anticoagulation and closure of veins deemed to be at high risk of initiating thromboemboli may be beneficial prior to a major operative resection. Multidisciplinary preoperative team meetings which include surgeons, anesthesiologists, interventional radiologists, hematologists, nurses and blood bank can be invaluable in preparing a team prior to large resections.

HEAD AND NECK

Maxillofacial Asymmetry

Soft tissue overgrowth is typically caused by facial infiltrating lipomatosis, which can be associated with maxillofacial bony asymmetry and dental malocclusion. The cheek, lip, and underlying bone can be enlarged and cause psychological distress.
Recommendations: Facial and dental arch asymmetry should be evaluated by a plastic or maxillofacial surgeon early in life. Dental abnormalities are addressed by a dentist. Work up includes an MRI of the head and brain.

Brain asymmetry

Multiple types of brain abnormalities have been described in CLOVES syndrome including hemimegalencephaly, cerebral asymmetry, cerebral white matter lesions, cortical dysplasia/migrational anomalies. These findings can be associated with seizures and developmental delay.
Recommendation: Cerebral abnormalities and neurologic symptoms should be evaluated by a neurologist or neurosurgeon. Work up includes an MRI of the brain.

SKIN

Capillary Malformation (CM)

Capillary malformations (also known as port wine stains) typically occur overlying truncal overgrowth and in the extremities. These stains are of limited clinical significance and usually require no treatment unless desired by the patient for cosmetic reasons. Lymphatic vesicles often coexist and may require therapy.

Recommendation: Flashlamp-pumped pulsed dye laser (FPDL) therapy can be used to lighten the color of capillary stains.

Epidermal Nevus and Moles
Epidermal nevi and moles in CLOVES are of limited clinical significance and may require no intervention beyond dermatologic screening and investigation of suspicious appearing moles.

Lymphatic Vesicles: See Lymphatic Malformation (LM).

CHEST

Truncal Lipomatous Overgrowth: See Overgrowth

Chest Wall Deformity
Chest wall deformity, which is typically associated with large overgrowth, should be evaluated by a pediatric surgeon. Associated scoliosis should be evaluated as described below.

ABDOMEN AND PELVIS

Gastrointestinal Involvement
Thickening of the anorectum and sigmoid colon is caused by circumferential venous and lymphatic malformation and may cause intestinal bleeding. Bleeding may also be caused by perianal lymphatic vesicles. Patients typically have slow, chronic bleeding leading to anemia. They may also experience episodes of acute, high volume bleeding. The presence of ectatic portomesenteric veins is associated with thrombosis and portal hypertension.
Splenomegaly and splenic lesions, thought to be multifocal lymphatic anomalies, can be present in CLOVES and typically of little clinical significance and therefore do not commonly require intervention.
Recommendations: Patients should be evaluated by a gastroenterologist and surgeon. Work up may include MRI study and colonoscopy. Anemia due to chronic bleeding may require iron supplementation or blood transfusions. Venous malformation can be treated with sclerotherapy, or surgical resection. For refractory bleeding, partial colectomy, anorectal mucosectomy, and coloanal pull-through may be considered. Ectatic portomesenteric veins, which can be visualized with MRI, CT scan or ultrasonography, can be managed initially with anticoagulation while surgical intervention is contemplated. A massively dilated, incompetent inferior mesenteric vein should be evaluated for ligation at its junction with the splenic vein to prevent siphoning of blood flow from the portal vein and resultant portal thrombosis.

Genitourinary Involvement
-Unilateral renal hypogenesis or agenesis and compensatory enlargement of the contralateral kidney are frequently present in CLOVES. Other findings include renal cysts, hydroureteronephrosis, heterogeneous renal parenchyma and renal malposition.

-There is an increased risk of Wilms tumors in CLOVES, occurring in ~3% of CLOVES patients studied. Wilms tumor prognosis is generally excellent, especially when found early.
-Enlargement and thickening of the urinary bladder in CLOVES may assume an elongated configuration with anterosuperior displacement. Venous malformation in the urothelial lining of the bladder and urethra may cause bleeding with urination (hematuria).
-Some patients experience functional urinary abnormalities or incontinence.
Recommendations: Children with CLOVES syndrome should undergo screening renal ultrasonography every 3 months until the age of 8 years to monitor for the development of Wilms tumor.
- We recommended an initial renal ultrasound in the neonatal period which also can be used as a baseline for Wilms tumor screening.
- Unilateral renal hypogenesis or agenesis is usually of little clinical significance.
- Functional abnormalities and hematuria should be evaluated by a urologist. Neurological causes of functional abnormalities should be excluded. Work up may include MRI study and cystoscopy. Venous lesions can be treated with laser coagulation.

Other abdominal findings include inguinal hernias, undescended testicles and ascites. Groin and scrotal masses appearing to be inguinal hernias may in fact be lymphatic malformations extending from the retroperitoneum. Resection can be challenging due to investment within the vital spermatic cord structures. This should be anticipated prior to scheduled herniorrhaphy so the surgeon is prepared to undertake meticulous and lengthy resection rather than a straightforward hernia repair.

EXTREMITIES

Asymmetric girth or length of the upper or lower extremities is a common finding in CLOVES. Diffuse overgrowth typically affects bones, muscles, nerves and fat. This enlargement may involve specific regions of the hand, foot, forearm, or leg and not necessarily the entire limb. Fat overgrowth in the affected portion of the limb may be markedly large and accounts for most of the enlargement.
Overgrowth and other musculoskeletal malformations may lead to secondary problems, such as early arthritis, contractures, stiff joint and neuromas. Capillary malformations and anomalous veins may also be present.

Developmental dysplasia of the hip and dislocation may exist particularly with large overgrowth of the pelvic and gluteal regions.
Knee deformities include valgus deformity, dysplasia, dislocation and chondromalacia patellae.
Common deformities of the foot include large, wide triangular foot with broad forefoot wide metatarsal spaces, wide sandal gap between first and second toes, lipomatous masses, macrodactyly (large toes), polydactyly (extra toes), syndactyly (fused toes), talipes, and furrowed soles. Lymphatic vesicles may affect the feet, especially the toes. These deformities may make finding appropriate shoe wear difficult.

Common deformities of the hands include broad spadelike asymmetric digits, macrodactyly, polydactyly, syndactyly, ulnar deviation of the digits and a laxity of collateral ligaments. Some digits and thumbs may be minimally enlarged and deviated. Significant deviation of the thumb is frequently seen Capillary malformations of the fingers are common. Fingers affected by macrodactyly may exhibit significant stiffness starting from birth. Fatty overgrowth of the forearm and hand may be seen. Dorsally-located lymphatic malformations of the digits may pose functional problems if large. Premature osteo-arthritis is common in the 3rd and 4th decades of life.

Recommendations: Limb abnormalities should be evaluated early in life. When present, these abnormalities should be followed by a team familiar with the relevant components of overgrowth.

-Leg length discrepancy: Standard follow up with physical exam and motion radiography should be established. Shoe lift and epiphysiodesis of long bones or digits may be considered.

-Debulking of the overgrown adipose and vascular tissues can provide functional and cosmetic benefits. Staged reconstruction is often indicated. Other treatment options include osteotomies, ostectomies, ray resection or amputations of markedly overgrown digits or limb.

Arthroscopy may be helpful in assessing the joint changes related to peri- and intra-articular vascular malformations. Sclerotherapy may minimize pain related to venous malformations. Hematologic evaluation prior to major orthopedic procedures is important to prevent thromboembolism.

Debulking of lymphatic malformations of the digits may help with function. Lymphatic malformations and fatty overgrowth of the palm are more difficult to address due to presence of tendons and neurovascular structures.

-Syndactyly and polydactyly treatment should be considered in light of functional requirements. If the syndactyly involves an overgrown, stiff digit, simultaneous amputation will provide ample skin for closure of the webspace.

-Deviation of the thumb can be challenging, possibly requiring osteotomy and/or amputation of the bulk or a border digit depending on the degree of deformity.

SPINAL/PARASPINAL REGION

Paraspinal Hypervascular-Lipomatous Overgrowth is characteristic of CLOVES syndrome. Elongated posterior mediastinal masses are located along the bilateral anterior paravertebral spaces and can mimic neurogenic tumors on cross-sectional imaging. Unlike overgrown tissue elsewhere, paravertebral lesions may be aggressive, and infiltrative with hypervascular, fast-flow malformations which may compromise the spinal cord and associated vessels. The tissue may extend into the spinal canal and cause compression of the thecal sac, spinal cord and nerve roots.

The natural history of these masses is variable. Many lesions remain stable in size and cause no signs or symptoms, while others can cause different types of neurologic injury, including mass effect on the spinal cord and nerve roots and high-flow/arteriovenous malformation, as described above.

Recommendations: Patients should be screened with an early MRI. Extension into the spinal canal should be evaluated and followed by a neurosurgeon. Work up includes a dedicated spinal MRI. The course of the behavior of these lesions should be evaluated with physical examination and annual spinal MRI study. Patients who develop signs of spinal cord dysfunction (extremity weakness, urinary incontinence, constipation) should be promptly evaluated and managed by a neurosurgeon. These masses may recur after partial surgical removal and follow-up is necessary.

Scoliosis in CLOVES tends to be progressive. It can be secondary to paraspinal-truncal soft tissue masses and disordered musculature, vertebral and other anomalies but can also be a separate, primary finding.
Recommendations: Patients with CLOVES syndrome should be screened for scoliosis by early MRI and routinely with physical examinations. Scoliosis should be treated per the usual recommendations by a pediatric orthopedic specialist. It can be difficult to manage with orthotic care due to truncal overgrowth. Surgical treatment may be indicated to prevent further deformity, pulmonary decompensation, and spinal cord injury.

Spinal-Paraspinal High Flow Anomalies: See Arteriovenous Malformation

Tethered Cord and Neural Tube Defects:
There is an increased risk of tethered spinal cord and neural tube defects (e.g. spina bifida and myelomeningocele) in CLOVES syndrome.
Recommendations: All patients with CLOVES syndrome should be evaluated clinically and screened for neural tube defects and tethered cord by spinal ultrasonography in the neonatal period. If early MRI study was performed and reliably characterized the spinal cord then an further ultrasonography is not necessary. If no imaging has been done at the time of first presentation, then a dedicated spinal MRI study is warranted.
Tethered spinal cord and neural tube defects should be managed and followed by a neurosurgeon with early detethering considered (if feasible) to prevent neurologic damage.

GUIDELINES FOR IMAGING STUDIES

Magnetic resonance imaging (MRI): is the imaging tool of choice to evaluate for most of the findings in CLOVES syndrome.
The following MRI sequences are performed for all vascular anomalies and overgrowth:

Axial Fat-Sat T1
Axial Fat-Sat T2
Coronal Fat-Sat T2
Sagittal Fat-Sat T2 (head and neck, extremities)
Contrast-enhanced: Axial Fat-Sat T1
MRA and MRV: may be useful in suspected dilated veins or high-flow lesions, but should not be performed as an alternative to the basic sequences.

Ultrasonography (US): Regular ultrasound images can be supplemented by color and spectral Doppler images whenever needed. Real-time exams are appropriate to study blood vessels, internal organs, screening for Wilms tumors, among others.
Computerized tomography (CT) scan: Due to the radiation risk, the use of CT scan is limited to certain indications such as imaging of bone disease and lungs.
Venography: Typically performed prior to interventions on abnormal veins.

CLOVES SYNDROME WORK GROUP

Disclosure: None of the members of the CLOVES Syndrome Work Group has and actual or reasonably perceived conflicts or a personal, professional, or business interest.

Core Work Group:
Ahmad Alomari, MD, MSc, FSIR
Meghan O'Hare, RN, MSN, CPNP
Kristine Specht, MD
Rudy Murillo, MD
Work Group:
Mary Landrigan-Ossar, MD, PhD. Anesthesiology
Marilyn Liang, MD. Dermatology
Harriet I. Paltiel, MD. Diagnostic Radiology
Victor L. Fox, MD. Gastroenterology/Nutrition
Steven J. Fishman, MD. General Surgery
Matthew Warman, MD. Genetics
Cameron C. Trenor III, MD. Hematology/Oncology
Horacio M. Padua, MD. Interventional Radiology
Gulraiz Chaudry, MD. Interventional Radiology
Raja Shaikh, MD. Interventional Radiology
Darren Benjamin Orbach, MD, PhD. Neurointerventional Radiology
Edward Robert Smith, MD. Neurosurgery
James R. Kasser, MD. Orthopedic Surgery
Samantha A. Spencer, MD. Orthopedic Surgery
Harry P.W. Kozakewich, MD. Pathology
Kyle Kurek, MD. Pathology
John B. Mulliken, MD. Plastic Surgery
Arin K. Greene, MD, MMSc. Plastic Surgery
Amir Taghinia, MD. Plastic Surgery
Joseph Upton, MD. Plastic Surgery
Erin Spera, MS, CPNP. VAC Nurse Practitioner,
Mary Beth Sylvia, MS, CFNP. VAC Nurse Practitioner
Cindy Kerr, MSN, CPNP. IR Nurse Practitioner
Brooke Corder, MSW, LICSW. Social Worker.
Kerri Welsh. VAC Program Coordinator

DEFINITIONS *

Adipose: Fatty
Hypogenesis/Agenesis: Under- or lack of development of an organ.
Anticoagulation: Hindering or preventing clot formation in blood vessels by treatment with an anticoagulant such as heparin.
Arteriovenous Malformation (AVM): Abnormal connection between arteries and veins, creating a shortcut for blood to bypass capillaries.
Asymmetry: Lack of symmetry or lack of proportion between body parts.
Bilateral: affecting both sides of the body.
Congenital: present at birth.
Contracture: Shortening of muscle or tendon due to deformity, or scarring of the tissue supporting the muscles, the joints, or a disorder of the muscle fibers themselves.
Cutaneous: related to skin.
Debulking: Removal of most or part of a tumor or a mass.
Early MRI: Magnetic resonance imaging study of the chest, abdomen, pelvis and lower extremities performed in the neonatal, early infancy or at the time of first presentation.
Embolization: Minimally invasive procedure to close abnormal blood vessels, typically performed by interventional radiologist under image guidance.
Epidermal nevus (plural: nevi): Flat, tan or raised, velvety patch of skin typically seen at birth or develop in early childhood. The nevus can become thicker and darker and are located on the neck, back, trunk or extremities.
Epiphysiodesis: Slowing bone growth by damaging the growth plate.
Genetic Counseling: A process, involving an individual or family, comprising evaluation to confirm, diagnose, or exclude a genetic condition, syndrome, or isolated birth defect; discussion of natural history and the role of heredity; identification of medical management issues; calculation and communication of genetic risks; provision of or referral for psychosocial support.
Genetic Testing: Analyzing DNA to look for a genetic alteration that may indicate an increased risk for developing a specific disease or disorder.
Hemimegalencephaly: Overgrowth of one side of the brain with large, asymmetric head which can be accompanied by seizures, partial paralysis, and developmental delay.
Hypervascular: Containing an excessive number of blood vessels, particularly arteries.
Imaging: Radiology. Using imaging technology to diagnose disease such as MRI, CT scan, ultrasound study and plain x-ray film.
Lipoma (Lipomatous): Benign growth of fatty tissue.
Lymphatic Malformation (LM): Lymph-filled channels, spaces or cysts caused abnormal development of the lymphatic system.
Macrocephaly (or megacephaly, megalocephaly): Large head. It does not necessarily indicate abnormality. In some families it is passed down through the generations.
Macrodactyly: Enlarged toes or fingers.
Malformation: Irregular or abnormal formation of structure that is congenital.
Megalencephaly (or macrencephaly): Abnormally large brain.
mTOR inhibitors: Drugs such as sirolimus which inhibit mammalian target of rapamycin (mTOR), an essential controller of cell growth, proliferation and new blood vessel formation.
Mutation: Any alteration in a gene which may cause disease or a benign, normal variant

Neural tube defects: Congenital malformations of the central nervous system and adjacent structures caused by incomplete closure of the neural tube during the early stages of embryonic development (such as anencephaly and spina bifida).
Overgrowth: Excessive growth or enlargement of tissue.
PIK3CA: A gene located on chromosome 3 and plays an important role in many cell activities, including growth, division and movement, production of new proteins, transport of materials within cells, cell survival and maturation of fat cells (adipocytes).
Phlebectasia: Dilation of the veins.
Post-zygotic mutation: Abnormality in chromosome that occurs after fertilization of the ovum by the sperm, often leading to mosaicism (two or more genetically distinct cell lines within the same organism).
Polydactyly: More than the normal number of toes or fingers.
Pulmonary embolism (PE): Sudden blockage in arteries of the lung caused by a blood clot that typically travels from the limb veins.
Sclerotherapy: Injection of a sclerosing agent into a venous or lymphatic malformation to produce inflammation and scarring followed by shrinkage, typically performed by interventional radiologist under image guidance.
Scoliosis: Sideways curve of the spine or backbone.
Skeletal: Relating to the skeleton (bones)
Splenomegaly: Enlarged spleen.
Syndactyly: Two or more digits are fused together.
Syndrome: A set of symptoms or conditions that occur together and are suggestive of a genetic cause.
Talipes, Clubfoot (or Talipes Equinovarus): Congenital condition in which the foot is turned inward and downward.
Truncal: Relating to the trunk (abdominal or chest wall).
Vascular Anomaly: Disorder of the vascular development, affecting arteries, veins, lymphatics, capillaries or a combination of these.
Venography: is a procedure in which x-ray images are taken after a special dye is injected into the veins to study the anatomy and blood flow.
Venous Malformation (VM): Abnormal venous channels and spaces caused by faulty development of the venous system. The two main types are spongiform VM and dilated veins (phlebectasia).
Viscera (Visceral): Internal organs of the body such as heart, lungs or liver.
Wilms tumor: Malignant tumor of the kidney that primarily affects children.

* Based on MedlinePlus, Genetics Home Reference, National Library of Medicine, NIH, Merriam-Webster and other medical dictionaries.

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- Oxford Centre for Evidence-Based Medicine (CEBM) at www.cebm.net/?o=1025

CONTACT US

The Boston Children's Hospital Vascular Anomalies Center (VAC) can be contacted anytime online, or by phone (Monday through Friday).

Vascular Anomalies Center
Fegan Building, Third Floor
Boston Children's Hospital
300 Longwood Avenue
Boston, MA 02115 USA
Tel: 617-355-5226
International: +1-617-355-5209
Fax: 617-730-0752
Email: vascular@childrens.harvard.edu