

Clinical Practice Guidelines for Klippel-Trenaunay Syndrome (KTS)

KTS Working Group

Vascular Anomalies Center (VAC)



Clinical Practice Guidelines for Klippel-Trenaunay Syndrome

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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.

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OVERVIEW

Klippel-Trenaunay syndrome (KTS) (OMIM # 149000) is a combination of slow-flow vascular malformations (capillary, lymphatic, and venous) in an overgrown limb. KTS is the prototype of complex overgrowth disorder associated with vascular anomalies and is the most common of these disorders. While there is phenotypic overlap, KTS has specific clinical and radiologic findings that separate it from other complex combination vascular anomalies syndromes such as Congenital Lipomatous Overgrowth, Vascular Malformations, Epidermal Nevis, Spinal/Skeletal Anomalies/Scoliosis syndrome (CLOVES), Proteus, Capillary Venous Malformation (CVM) with overgrowth, Diffuse Capillary Malformation with overgrowth (DCMO), and Parkes Weber syndrome.

KTS manifests as a cluster of congenital malformations affecting the limb(s) and pelvis. It typically affects the lower extremity unilaterally. Nevertheless, KTS may occasionally affect the upper extremity or both legs. Upper extremity presentation has previously been referred to as thoracic or truncal KTS; many of those patients are now diagnosed as CLOVES. Involvement of the gastrointestinal and genitourinary tracts is also common in KTS.

Institutional knowledge and experience of our interdisciplinary Vascular Anomalies Center (VAC) at Boston Children's Hospital was consolidated through managing and studying a large cohort of patients with KTS. Here we provide a review of the clinical presentation and diagnostic studies, and provide management guidelines, where appropriate, to help care for patients with this syndrome. These are organized below according to the involved system or organ.

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 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.

DEFINITION

KTS has often been used as a generic diagnosis referring to a heterogeneous group of vascular anomalies with overgrowth. Despite the presence of more than 1,000 published articles, lack of clear diagnostic criteria, misdiagnoses and misconceptions are still common in the published literature about KTS. Specific clinical and radiologic findings separate it from other complex combination vascular anomalies syndromes such as CLOVES, Proteus, CVM with overgrowth, DCMO, and Parkes Weber syndrome.

KTS is strictly defined as a combination of slow-flow vascular malformations (capillary,

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lymphatic, and venous) in an overgrown limb. This definition allows for better understanding of the disease, distinction from other disorders and better treatment recommendations.

The following conditions can share some features with KTS and may be considered in the differential diagnosis: Lymphedema, lymphatic malformation, venous malformation, capillary malformation (with or without overgrowth), diffuse capillary malformation with overgrowth (DCMO), hemihypertrophy, Parkes Weber syndrome, lipedema, infantile hemangioma, kaposiform hemangioendothelioma and lipofibromatosis.

GOALS

Here we list the clinical features of KTS and provide management guidelines, where appropriate, based on the best available evidence. These guidelines aim to assist practitioners caring for patients with KTS and improve care by outlining some of the various clinical aspects of this uncommon syndrome and our current recommendations for management. The recommendations are organized by type and anatomical areas affected. 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

Early Treatment

As a general rule, we advocate an early treatment approach to KTS in which lesions that potentially lead to major morbidity are preemptively characterized and treated.

Referral

Given its rarity and complexity, patients with KTS 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.

Magnetic Resonance Imaging

KTS patients may benefit from magnetic resonance imaging (MRI) of the abdomen, pelvis and lower extremities performed in the early infantile period or at the time of initial presentation. This will help define deeper components (e.g. massive venous ectasia, lymphatic and venous anomalies, gastrointestinal and genitourinary involvement), as well as characterize the limb overgrowth and extension into the limb girdle and pelvis.

If the study 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. Specific imaging sequences are outlined under Guidelines for Imaging KTS later in this paper.

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Genetics

KTS is diagnosed on the basis of clinical findings. Deeper tissue involvement is elucidated by imaging findings. The discovery of the *PIK3CA* gene as the cause of KTS opens up the possibility of a medical therapy; PI3K and mTOR inhibitors are actively being investigated. Currently there are commercially available genetic tests for *PIK3CA* mutations. At an investigative level, droplet digital PCR can reliably detect the most common mutations. A positive test can confirm the diagnosis, whereas a negative test result cannot exclude the diagnosis.

Currently, the presence or absence of a *PIK3CA* mutation does not define the diagnosis of KTS or influence management.

Nutritional Support

KTS patients with poor weight gain, failure to thrive may benefit from nutritional consultation, supplementation and ongoing support and reassessment.

Overgrowth Issues: Wilms Tumor/Malignancy Risks

In contrast to other *PIK3CA* disorders we have not seen evidence of early or atypical malignancy in patients with KTS. We have recently discovered a risk of Wilms tumor in CLOVES but have not seen this associated yet in KTS.

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 cope with the 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 KTS vary in size from small cutaneous vesicles to large deep lesions. The clinical consequences and treatment of these lesions vary accordingly.

Commonly encountered forms of LM in KTS include:

1. Macrocystic LM, which may be comprised of a single or few cysts in the limb, pelvis or abdomen. These lesions are prone to recurrent flare-ups (due to infection and intralesional bleeding), swelling and chronic pain.
2. Microcystic LM is typically mixed within the fatty overgrowth of the limb, gluteal or pelvic-perirectal area. Infection can be recurrent and may cause sepsis, significant swelling and pain.

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3. Cutaneous lymphatic lesions typically present as skin vesicles, nodules on plaques affecting the skin particularly within and around the capillary stain on the lateral aspect of the limb. Involvement of the foot, toes and perianal regions is frequent. These lesions may contain clear lymph or more commonly solid black or bloody contents. Cutaneous LM is prone to lymph leak, bleeding and infection.
4. Typically, KTS manifests as a combination of these 3 forms.

Recommendation: Sirolimus is increasingly used to control lymphatic complications in KTS. Focal complications are often managed with procedures. Extensive or refractory lymphatic issues should prompt discussion of Sirolimus therapy. Macrocystic LMs are amenable to sclerotherapy, which can be electively performed with other procedures by interventional radiology under the same anesthesia.

Large complex lymphatic malformations associated with overgrowth may benefit from surgical debulking. A combined approach with sclerotherapy and resection can be beneficial in selected patients.

Proper hygiene and skin care is imperative for cutaneous and mucosal lymphatic vesicles. These can be treated with sclerotherapy (including the use of bleomycin) or CO2 laser photovaporization.

Recommendation: Infected LMs should be promptly evaluated with early initiation of antibiotic treatment. Some patients may require admission for treatment with IV antibiotics, which can be switched to oral route if signs of sepsis are excluded. Patients typically require a prolonged course of treatment for a minimum of 21 days of therapy.

Infected macrocystic LMs can be percutaneously drained and treated with sclerotherapy during the same admission which can often speed recovery from the infection.

Recommendation: Cutaneous vesicles can be treated electively with different methods including CO2 laser photovaporization and Bleomycin sclerotherapy.

Venous Malformation (VM)(Phlebectasia)

Phlebectasia (dilatation of veins) in KTS is typically caused by persistent large embryonic veins. These anomalous veins include the sciatic vein, the marginal venous system (MVS) and occasional gluteal and pelvic-retroperitoneal venous channels. Phlebectasia may also affect orthotopic veins including the small saphenous veins, aneurysmally dilated popliteal-femoral junction and dilated inferior vena cava (IVC, megacava).

These incompetent veins can attain a considerable size with gravitational pooling and stagnation of blood in the lower limb resulting in pain, increased risk of thromboembolism and, in severe cases, postural hypotension. The risk of thromboembolism is higher around surgical intervention on the affected limb.

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The marginal venous system (MVS) is anatomically related to the capillary (port wine) stain and is largely located within the subcutaneous layer of the lateral aspect of the lower extremity. The MVS commences in the dorsum of the foot and ascends proximally to variable levels and may divide into multiple channels. It commonly communicates via large perforators with the deep (tibial, popliteal, femoral and iliac) veins and superficial (saphenous) veins.

The sciatic vein, typically the largest venous channel in the limb, starts at the level of the knee and accompanies the sciatic nerve caudally to terminate into large inferior gluteal-internal iliac veins. The size of this vein can be underestimated due to external compression as it passes under the piriformis muscle at the greater sciatic notch. Due to lack of high-flow component, signs of hyperdynamic flow and cardiac overload are absent.

Due to the large size of the anomalous veins, venous return from the limb is preferentially diverted from the smaller, underdeveloped deep venous system into these anomalous, valveless veins.

In addition, patients may develop intralesional painful clots (thrombophlebitis). Patients with extensive venous anomalies may have altered blood tests (low fibrinogen, high D-dimer, prolonged PT/PTT) due to stagnant or slowed blood flow and increased activation of the clotting cascade as an indicator of blood clot formation within the anomalous channels.

Recommendation: Graduated compression stockings improve venous hemodynamics and symptoms. Custom-fit compression hoses (e.g. Class III 30-40 mm Hg, thigh-high with waist attachment or pantyhose style) may also reduce the risk of superficial thrombophlebitis.

Recommendation: Regular follow up should be maintained with clinical, psychological and social specialists familiar with the disorder. Pain management may be needed for chronic pain but should minimize chronic opiate use and maximize adjunctive therapy (e.g. biofeedback, therapeutic massage, gabapentin). Social support and education of the families and patients are invaluable parts of the multidisciplinary treatment.

Recommendation:

1. All patients should undergo preoperative imaging to assess the venous system. If MRI has not been performed, proper imaging to evaluate the venous anatomy prior to any invasive intervention is strongly recommended. Ultrasonography may demonstrate many of the anomalous veins including the MVS, popliteal-femoral and short saphenous veins.
2. Closure of the dilated veins may reduce the risk of thromboembolism, particularly prior to surgical procedures. We also hypothesize that it may divert the limb venous return into the deep venous system and improve venous development and hemodynamics. We recommend closing specific dilated veins early in life using minimally invasive techniques

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such as embolization, endovenous laser, phlebectomy and sclerotherapy by an experienced interventional radiologist.

3. KTS patients should have hematology evaluation including basic coagulopathy work-up pre-procedurally to allow consideration of anticoagulation. KTS patients with large anomalous veins and increased risk of venous thromboembolism may benefit from prophylactic anticoagulation during the perioperative period. Anticoagulation is often recommended both before and after the procedure. Placement of temporary IVC filters may also be considered. Patients with positive family histories or extensive thrombotic complications may warrant thrombophilia evaluation.

4. Prior to invasive surgical procedures, patients with severe KTS may benefit from evaluation by an anesthesiologist and multidisciplinary team to achieve optimization of physical status.

5. Thrombophlebitis can be treated with limb elevation, compression stockings, gradual ambulation, warm compresses, and nonsteroidal anti-inflammatory drugs.

At our institution, abnormal intrafascial veins (e.g. ipsilateral internal iliac, inferior gluteal-sciatic veins) are embolized using coils and other permeant tools. Heat-based treatment methods (e.g. laser or radiofrequency ablation) should be avoided in the sciatic vein due to risk of nerve injury. Anomalous superficial veins (e.g. marginal and short saphenous veins) can be treated with diode or Nd:YAG endovenous laser treatment.

Prior to this procedure, the deep veins can be usually studied with “diversion venography” since passive opacification of the deep venous system in classic venography is often insufficient and can be misleading due to preferential flow in the large anomalous veins.

Sclerotherapy may minimize the size and pain related to superficial venous channels, particularly if pain is related to thrombophlebitis.

Capillary Malformation (CM)

Capillary malformation (also known as port wine stain) is typically present on the lateral aspect of the extremity, particularly on the thigh, knee and upper calf regions. Smaller stains can be found on the foot, toes and other areas. Isolated CMs are of limited clinical significance and usually require no treatment unless desired by the patient for cosmetic purposes. Lymphatic vesicles often coexist with CM and may require therapy. A skin graft can be utilized if excision of a larger CM is desired.

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

ABDOMEN AND PELVIS

Gastrointestinal Involvement

Marked thickening of the anorectum and sigmoid colon is caused by circumferential venous

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and lymphatic malformation. This often causes chronic bleeding and anemia. Bleeding may also be caused by perianal lymphatic vesicles. While bleeding is typically slow and chronic, some patients may experience occasional episodes of acute, high volume venous bleeding.

The presence of ectatic portomesenteric (e.g. inferior or superior mesenteric) veins can cause thrombosis and portal hypertension.

Splenomegaly and splenic lesions, thought to be multifocal lymphatic anomalies, can be present in KTS and usually carry no or little clinical significance and therefore do not commonly require intervention. Rarely, splenectomy can be indicated for massive splenomegaly.

Recommendation: Patients should be evaluated by a gastroenterologist and general surgeon. Evaluation may include an MRI study and colonoscopy. Anemia due to chronic bleeding may require iron supplementation or blood transfusions. Sirolimus can improve gastrointestinal (GI) bleeding in patients with KTS. Anorectal bleeding due to malformation can also be treated with sclerotherapy, or surgical resection. For refractory bleeding, partial colectomy, anorectal mucosectomy, and coloanal pull-through may be considered.

1. The presence of ectatic portomesenteric veins should be studied with cross sectional imaging.
2. Large inferior or superior mesenteric veins can be managed initially with anticoagulation while surgical intervention is contemplated. A massively dilated, incompetent 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

Enlargement, hypotonia and thickening of the urinary bladder wall in KTS may assume an elongated configuration with anterosuperior displacement. Venous anomalies in the urothelial lining of the bladder and urethra may cause hematuria.

Recommendation: Functional abnormalities and hematuria should be evaluated by an urologist. Bleeding venous lesions can be treated with laser coagulation. Other abdominal findings include inguinal hernias, undescended testicles, hydrocele, scrotal overgrowth and lymphatic malformations. Resection can be challenging due to investment within the vital spermatic cord structures.

MUSCULOSKELETAL MALFORMATIONS

Limb enlargement in KTS is largely composed of diffuse fat overgrowth within the subcutaneous layer resulting in asymmetric girth or length of the lower extremities. Muscle involvement in KTS is typically overlooked despite the presence of significant abnormalities including fibrofatty changes and large intramuscular veins.

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Overgrowth and other musculoskeletal malformations may lead to secondary problems, such as early arthritis, contractures and stiff joint, muscle atrophy and weakness.

Foot abnormalities in KTS include massive overgrowth, lymphatic vesicles, capillary stains and variable anomalies of the toes. These deformities may make finding appropriate shoe wear difficult.

Recommendation: 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. Closure of the MVS and associated ectatic veins that pose risk of thromboembolism should be closed prior to any surgical intervention.

1. 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.
2. 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 toes or limb.
3. Arthroscopy may be helpful in assessing the joint changes related to peri- and intra-articular osseous or vascular malformations.
4. For muscle atrophy and weakness limb underuse, physical therapy can be considered.

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Summary of Clinical Practice Guidelines for KTS

Clinical Feature	Management Recommendation
Lymphatic malformation (LM)	-Macrocystic LM: sclerotherapy -Large complex or combined LM with fatty overgrowth: Surgical debulking -Vesicles: CO2 laser or sclerotherapy -Extensive or refractory: Sirolimus
Infection	-Localized: Antibiotics -Sepsis: IV antibiotics and supportive measures -Recurrent infection: Prolonged prophylactic antibiotics, Sirolimus
Venous malformation (VM) (Phlebectasia)	-Hematologic evaluation pre-procedurally -Compression garments -Embolization, laser and sclerotherapy -Perioperative prophylactic anticoagulation -IVC filter insertion
Capillary malformation (CM)	Pulsed Dye Laser -Resection
Massive overgrowth	-Debulking -Amputation
Hematuria	-Cystoscopy and laser coagulation
Gastrointestinal (GI) bleeding	-Colonoscopy -Sclerotherapy -Partial colectomy/anorectal mucosectomy/coloanal pull-through -Sirolimus
Ectatic portomesenteric veins	-Surgical ligation
Extremity girth and length discrepancy	-Significant leg length discrepancy: Epiphysiodesis and orthopedic follow up
Foot deformities	-Surgical: Partial or ray resections, amputations of markedly overgrown and deformed digits -Debulking
Muscle atrophy and weakness	-Physical therapy
Psychological issues	-Psychiatry, psychology, social work, support groups

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GUIDELINES FOR IMAGING OF KTS

Magnetic resonance imaging (MRI): The imaging tool of choice to evaluate for most of the findings in KTS.

The following MRI sequences are recommended for vascular anomalies and overgrowth:

- Axial Fat-Sat T1
- Axial Fat-Sat T2
- Coronal Fat-Sat T2
- Sagittal Fat-Sat T2
- Contrast-enhanced: Axial Fat-Sat T1
- MR Venography (MRV): may be useful for imaging deeply-located dilated veins (e.g. saphenous, iliac and IVC). However, MRV may underestimate the status of the deep venous system due to flow steal by the larger anomalous veins. MRV 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 veins, venous thrombosis, lymphatic malformation, and internal organs, among others. US is an invaluable tool for guidance of minimally invasive procedures.

Computerized tomography (CT) scan: Due to the radiation risk, the use of CT scan is limited to certain indications such as imaging of the bone and abdomen as well as acute pulmonary embolism.

Diversion Venography: Typically performed prior to interventions on abnormal veins.

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BOSTON CHILDREN'S HOSPITAL KTS WORKING GROUP

Disclosure: *None of the members of the KTS Working Group has an actual or reasonably perceived conflict or a personal, professional, or business interest.*

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DEFINITIONS *

Adipose: Fatty

Anticoagulation: Hindering or preventing clot formation in blood vessels by treatment with an anticoagulant such as heparin.

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.

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.

Hypogenesis/Agenesis: Under- or lack of development of an organ.

Imaging: Radiology. Using imaging technology such as MRI, CT scan, ultrasound study and plain x-ray film to diagnose disease.

Lipoma (Lipomatous): Benign growth of fatty tissue.

Lymphatic malformation (LM): Lymph-filled channels, spaces or cysts caused by abnormal development of the lymphatic system.

Macroductyly: Enlarged toes or fingers.

Malformation: Irregular or abnormal formation of a structure that is congenital.

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.

Overgrowth: Excessive growth or enlargement of tissue.

PIK3CA: A gene located on chromosome 3 that 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 vein.

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).

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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.

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.

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: <https://www.nlm.nih.gov/medlineplus/> ; Genetics Home Reference: <http://ghr.nlm.nih.gov/glossary> ; National Library of Medicine: <https://www.nlm.nih.gov/> ; National Institutes of Health: <http://www.nih.gov/> ; *Merriam-Webster Dictionary and Thesaurus* and other medical dictionaries.

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REFERENCES

1. Alomari AI. Diversion venography—a modified technique in Klippel-Trenaunay syndrome: initial experience. *J Vasc Interv Radiol.* 2010;21(5):685–689.
2. Alomari AI. Klippel-Trenaunay syndrome: imaging and treatment options. In: *Controversies and Updates in Vascular Surgery (Controverses et Actualités en Chirurgie Vasculaire)*, Edizioni Minerva Medica, Turin, Italy;2010:433–441.
3. Christison-Lagay ER, Fishman SJ. Vascular anomalies. *Surg Clin North Am* 2006;86(2):393-425.
4. Enjolras O, Chapot R, Merland JJ. Vascular anomalies and the growth of limbs: a review. *J Pediatr Orthop B.* 2004;13(6):349–357.
5. Fishman SJ, Shamberger RC, Fox VL, Burrows PE. Endorectal pull-through abates gastrointestinal hemorrhage from colorectal venous malformations. *J Pediatr Surg.* 2000;35(6):982–984.
6. Greene AK, Kieran M, Burrows PE, Mulliken JB, Kasser J, Fishman SJ. Wilms Tumor Screening Is Unnecessary in Klippel-Trenaunay Syndrome. *Pediatrics.* 2004. 113(4): e326-e329.
7. Jacob AG, Driscoll DJ, Shaughnessy WJ, Stanson AW, Clay RP, Gloviczki P. Klippel-Trénaunay syndrome: spectrum and management. *Mayo Clin Proc.* 1998;73(1):28-36.
8. Kulungowski AM, Fishman SJ. Management of combined vascular malformations. *Clin Plast Surg.* 2011;38(1):107–120.
9. Kulungowski AM, Fox VL, Burrows PE, Alomari AI, Fishman SJ. Portomesenteric venous thrombosis associated with rectal venous malformations. *J Pediatr Surg.* 2010;45(6):1221–1227.
10. Kurek KC, Luks VL, Ayturk UM, Alomari AI, Fishman SJ, Spencer SA, Mulliken JB, Bowen ME, Yamamoto GL, Kozakewich HP, Warman ML. Somatic Mosaic Activating Mutations in PIK3CA Cause CLOVES Syndrome. *Am J Hum Genet.* 2012. 90(6): 1108-1115.
11. Lee A, Driscoll D, Gloviczki P, Clay R, Shaughnessy W, Stans A. Evaluation and management of pain in patients with Klippel-Trenaunay syndrome: a review. *Pediatrics.* 2005;115(3):744–749.
12. Luks VL, Kamitaki N, Vivero MP, Uller W, Rab R, Bovée JV, Rialon KL, Guevara CJ, Alomari AI, Greene AK, Fishman SJ, Kozakewich HP, Maclellan RA, Mulliken JB, Rahbar R, Spencer SA, Trenor CC 3rd, Upton J, Zurakowski D, Perkins JA, Kirsh A, Bennett JT, Dobyns WB, Kurek KC, Warman ML, McCarroll SA, Murillo R. Lymphatic and Other Vascular Malformative/ Overgrowth Disorders Are Caused by Somatic Mutations in PIK3CA. *J Pediatr.* 2015;166(4):1048-1054
13. Mattassi R, Vaghi M. Management of the marginal vein: current issues. *Phlebology.* 2007;22(6):283–286.
14. Oxford Centre for Evidence-Based Medicine (CEBM) at www.cebm.net/?o=1025 .
15. Samuel M, Spitz L. Klippel-Trenaunay syndrome: clinical features, complications and management in children. *Br J Surg.* 1995;82(6):757–761.

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16. Sapp JC, Turner JT, van de Kamp JM, van Dijk FS, Lowry RB, Biesecker LG. Newly delineated syndrome of congenital lipomatous overgrowth, vascular malformations, and epidermal nevi (CLOVE syndrome) in seven patients. *Am. J. Med. Genet. A.* 2007;143A(24):2944-2958.
17. Schook CC, Mulliken JB, Fishman SJ, Alomari AI, Grant FD, Greene AK. Differential diagnosis of lower extremity enlargement in pediatric patients referred with a diagnosis of lymphedema. *Plast Reconstr Surg.* 2011;127(4):1571-1581.
18. Servelle M. Klippel and Trénaunay's syndrome. 768 operated cases. *Ann Surg.* 1985;201(3):365-373.
19. Uller W, Fishman SJ, Alomari AI. Overgrowth syndromes with complex vascular anomalies. *Semin Pediatr Surg.* 2014;23(4):208-215.

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