DIAGNOSIS AND MANAGEMENT OF CEREBRAL VENOUS THROMBOSIS

A Scientific Statement from the American Heart Association

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STROKE COUNCIL PROFESSIONAL EDUCATION COMMITTEE

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BACKGROUND ON CEREBRAL VENOUS THROMBOSIS

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- Defined as the presence of a blood clot in the dural venous sinuses, cerebral veins, or both
- Represents 0.5% to 3% of strokes
- Predominantly affects
  - Individuals younger than 55
  - 2:1 female-to-male predominance
- Most survive without physical disability but chronic symptoms (headaches, cognitive concerns, etc.) not uncommon
- Most common factors associated with poor prognosis
  - Advanced age
  - Active cancer
  - Decreased level of consciousness
  - Intracerebral hemorrhage

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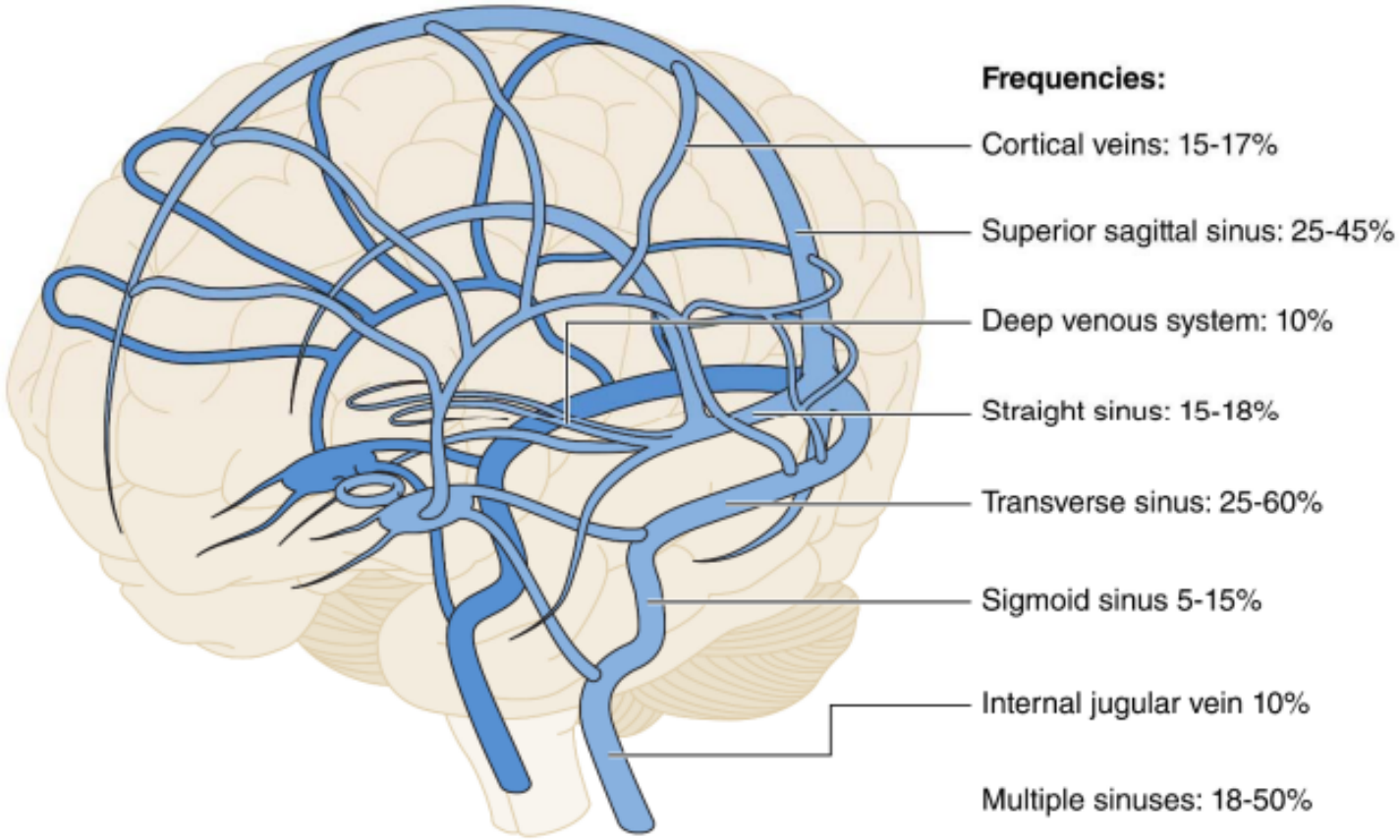
MOST FREQUENT LOCATIONS OF CEREBRAL VENOUS THROMBOSIS



Legend: Prevalence of sinus involvement in CVT. Percentages may be higher than 100% as many patients may have more than one sinus involved.[1-3] Please note that internal jugular vein thrombosis represents its concomitant prevalence with CVT (not in isolation).

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CLINICAL PRESENTATION OF CEREBRAL VENOUS THROMBOSIS

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- Headache is the most common symptom, occurring in almost 90% of cases
- Focal neurologic deficits (20-50%)
- Seizure (20-40%)
- Encephalopathy and coma (up to 20%)
- Symptoms related to increased intracranial pressure
  - Nausea
  - Transient visual obscurations or vision loss (13-27%)
  - Papilledema
  - Diplopia (6-14%)
  - Other cranial neuropathies (6-11%)
- Most symptoms tend to occur more insidiously than other stroke types with majority peaking more than 48 hours after onset
- Minority with acute onset of thunderclap headache or subarachnoid hemorrhage (<5%), or acute onset focal neurologic deficits (5-40%)

PREDISPOSING FACTORS FOR CEREBRAL VENOUS THROMBOSIS

PREDISPOSING FACTORS FOR CEREBRAL VENOUS THROMBOSIS

- Predisposing factor(s) for cerebral venous thrombosis are identified in the majority of patients
  - Oral contraception/hormonal therapies (~8-fold risk)
  - Pregnancy/puerperium
  - Acquired thrombophilias
  - Genetic thrombophilias
  - Infections (COVID-19, head/neck)
  - Dehydration
  - Medications
  - Vaccine-induced thrombotic thrombocytopenia

Table 1: Predisposing factors or medical conditions associated with CVT

	Transient	Chronic
Sex—specific and Transgender hormonal treatment	Oral contraceptive (54-71%) Pregnancy/Post-partum (11-59%) Hormone replacement therapy (4%)	Hormone replacement therapy Hormone therapy for transfeminine or transmasculine individuals
Other morbidity	Head and neck infections (8-11%) Dehydration (2-19%) Anemia Sepsis Respiratory infections Covid-19 (7.6%)	Obesity (23%) Anemia (9-27%) Other systemic diseases (thyroid disease, nephrotic syndrome, inflammatory bowel disease) 1-2%
Other medications	Corticosteroids L-asparaginase Thalidomide Tamoxifen	
Malignancy		Myeloproliferative disorders (2-3%) Other malignancy (7%)
Auto-immune		Antiphospholipid antibody syndrome (6-17%) Connective tissue disease (Systemic lupus erythematosus, Behcet's. Sarcoidosis) (1%)
Other genetic thrombophilia (31-41%)		Prothrombin 20210A mutation Factor V Leiden mutation MTHFR (C677T) polymorphism Antithrombin deficiency, JAK2, Protein C or Protein S deficiency (can be genetic or acquired)
Mechanical	Head trauma (1-3%) Neurosurgical procedures Jugular vein catheterizations (1-2% iatrogenic)	Compressive lesions of venous sinus (meningioma) Dural arteriovenous fistula

LONG-TERM SYMPTOMS OF CEREBRAL VENOUS THROMBOSIS AND RECURRENCE RATE

LONG-TERM SYMPTOMS OF CEREBRAL VENOUS THROMBOSIS

- 80–90% Achieve functional independence (modified Rankin Score 0–2)
- Despite high rates of functional independence, high prevalence of residual symptoms
  - Headaches
  - Cognitive concerns
  - Mood
  - Fatigue
- Epilepsy can affect over 10% and is more likely in those with seizures at onset, decreased level of consciousness or focal deficits, hemorrhagic lesions at baseline, or superior sagittal sinus involvement
- Dural arteriovenous fistula can be a complication or precipitant of cerebral venous thrombosis

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RECURRENCE RATES AFTER CEREBRAL VENOUS THROMBOSIS

- Recurrent venous thromboembolism risk after CVT ranges between 1-4%/year
- Recurrent CVT risk reported to be <1-2%/year
  - Higher risk for those with severe thrombophilia, history of VTE, those without identified precipitants
- Compared to age- and sex-matched controls those with CVT have higher risk of:
  - Recurrent venous thromboembolism
  - Ischemic stroke
  - Major bleeding
  - Mortality

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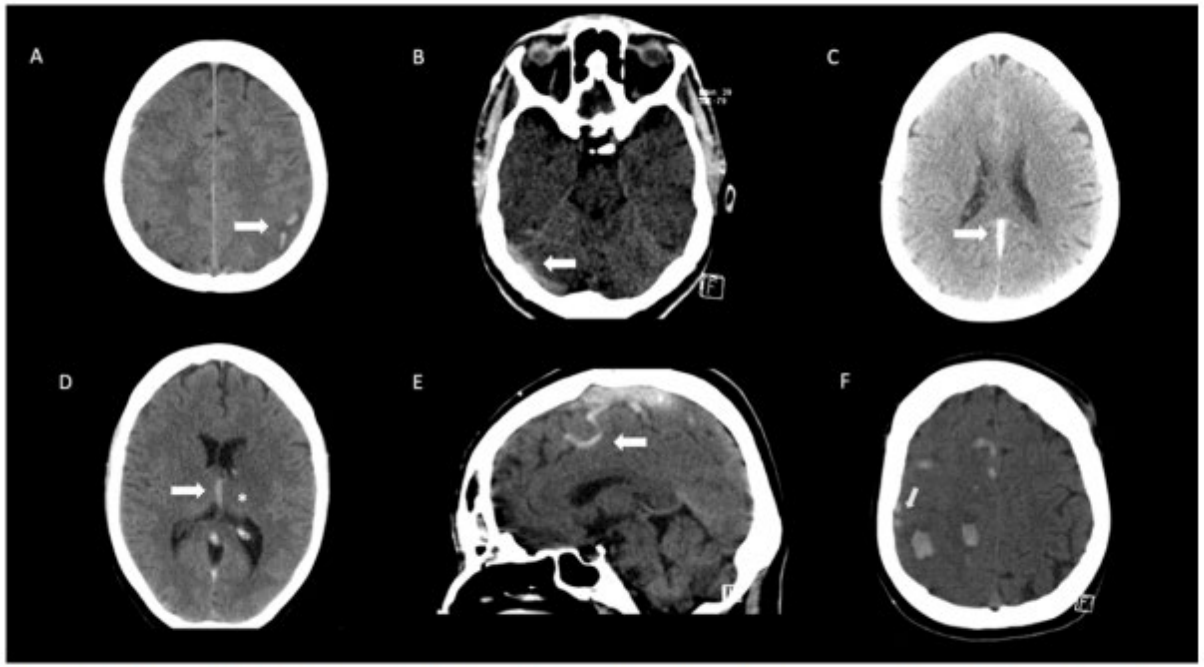
BRAIN AND VASCULAR IMAGING FOR THE DIAGNOSIS OF CEREBRAL VENOUS THROMBOSIS

BRAIN AND VASCULAR IMAGING FOR THE DIAGNOSIS OF CVT

CONVENTIONAL NON-CONTRAST CT HEAD

- Hyperattenuation caused by thrombus (dense vessel sign)
  - Can be present up to 14 days after symptom onset
- Hypodensities not conforming to arterial territories or present bilaterally
- Hemorrhage present in up to 40%
- Cashew-nut sign: juxtacortical C-shaped hyperdensity has high specificity for CVT
- CT Head test characteristics
  - Sensitivity of 0.79
  - Specificity of 0.90

Figure 2. Typical findings of CVT on NCCT



Legend: Panel A: Left sided juxtacortical C-shaped hemorrhages; Panel B: Transverse sinus thrombosis; Panel C: Straight sinus thrombosis; Panel D: Internal cerebral vein thrombosis (arrow) and left thalamic hypodensity (star). Panel E: Cord sign (arrow) and hyperdense sagittal sinus thrombosis (star); Panels F: Multiple small hemorrhages in same patient as Panel E, arrows indicate cord sign

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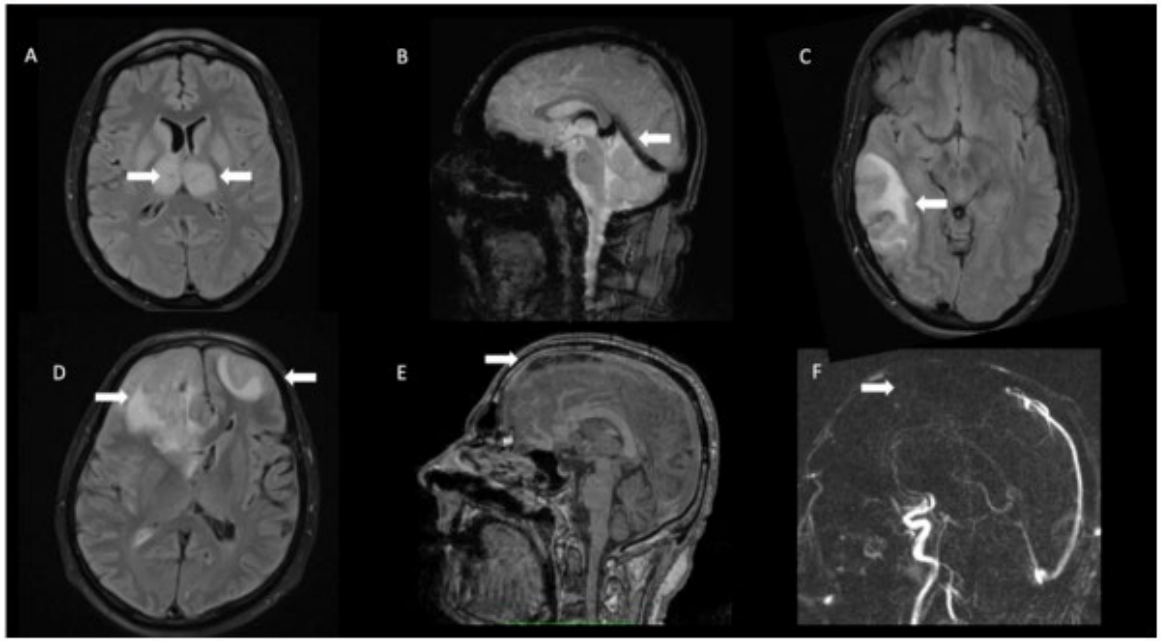
BRAIN AND VASCULAR IMAGING FOR THE DIAGNOSIS OF CVT

MRI BRAIN

- Evolution of thrombus on MRI is dynamic and signal intensity of the thrombus over time is similar to that of hematoma
- Helpful to corroborate T1/T2 sequences with gradient-recalled echo (GRE), susceptibility-weighted imaging (SWI) sequences or contrast enhanced-MRV
  - Thrombosed blood creates blooming artifact on GRE/SWI which leads to specificity and specificity approaching 100%
- MRI more sensitive than CT in detection of parenchymal brain lesions, such as venous infarctions
- MRI Brain test characteristics
  - Sensitivity 0.82
  - Specificity 0.92

Figure 3. Typical findings of CVT on MRI



Legend: Panel A: Bilateral thalamic hyperintensity (arrows) on FLAIR in a patient with deep cerebral vein thrombosis; Panel B: Susceptibility weighted imaging shows hypointensity of the straight sinus (arrow), vein of Galen and internal cerebral veins; Panel C: Venous infarction due to transverse sinus thrombosis with heterogenous FLAIR hyperintensity (arrow); Panel D: Bilateral FLAIR hyperintensities (arrows) with mass effect in a patient with superior sagittal sinus thrombosis (arrow), shown in E on a contrast-enhanced T1 sequence and F. absent venous filling defect (arrow) with a phase-contrast MRV

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BRAIN AND VASCULAR IMAGING FOR THE DIAGNOSIS OF CVT

- CT venography or MR venography are optimal tests to confirm diagnosis of CVT
- CT venography allows for clear depiction of superficial and deep cerebral venous system with thrombi present as filling defects
- CT venography has lower sensitivity than MRI for cortical vein thrombosis
- MR venography can be performed with or without contrast
  - Use of gadolinium contrast allows for direct assessment of luminal filling and increases sensitivity of detection of thrombus within smaller veins
- Time-of-flight and phase-contrast MR venography techniques prone to artifact secondary to complex flow
- Contrast-enhanced MR venography has comparable sensitivity and specificity to CT venography but provides better characterization between low flow state and hypoplastic signus.
- Contrast-enhanced MR venography and GRE or SWI are recommended for diagnosing cortical vein thrombosis

THERAPEUTIC ADVANCES IN THE MANAGEMENT OF CEREBRAL VENOUS THROMBOSIS

THERAPEUTIC ADVANCES IN THE MANAGEMENT OF CVT - ANTICOAGULATION

- Objectives of anticoagulation for CVT are:
  - Prevent thrombus growth
  - Facilitate recanalization
  - Prevent recurrent venous thromboembolism (VTE)
- Previous guidelines suggest initial use of low molecular weight heparin (over unfractionated heparin) followed by:
  - 3-12 months of oral vitamin K antagonists for 3-12 months in context of transient risk factors
  - Indefinite oral vitamin K antagonist therapy in context of chronic major risk factors for thrombosis or recurrent VTE
- Emerging evidence suggest that direct oral anticoagulants (DOACs) may be a reasonable alternative to oral vitamin K antagonists
  - No significant differences in recurrent VTE
  - Potentially lower risk of major hemorrhage with DOACs
  - Similar rates of complete recanalization
- Persistent areas of equipoise:
  - Need for lead-in heparinization and duration of lead-in heparinization
  - Need for acute VTE dosing of DOACs
  - Who are best candidates for DOACs
  - Use of repeated imaging to guide duration of anticoagulation

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THERAPEUTIC ADVANCES IN THE MANAGEMENT OF CVT – REPERFUSION & DECOMPRESSIVE CRANIECTOMY

- Endovascular treatment of CVT offers theoretically faster recanalization and could include
  - Mechanical thrombectomy
  - Intrasinus thrombolysis
  - Combination of mechanical thrombectomy and intrasinus thrombolysis
  - Intrasinus stenting
- Trials have yet to demonstrate that endovascular treatment confers benefit over receiving standard anticoagulation and may be associated with higher mortality
- Endovascular therapy is more typically used as a “rescue treatment” for patients experiencing clinical deterioration or failed or have contraindications to standard therapy
- Decompressive craniectomy should be offered to patients with acute severe CVT and parenchymal lesions with impending herniation as a life-saving therapeutic approach
  - May decrease mortality and improve functional outcomes

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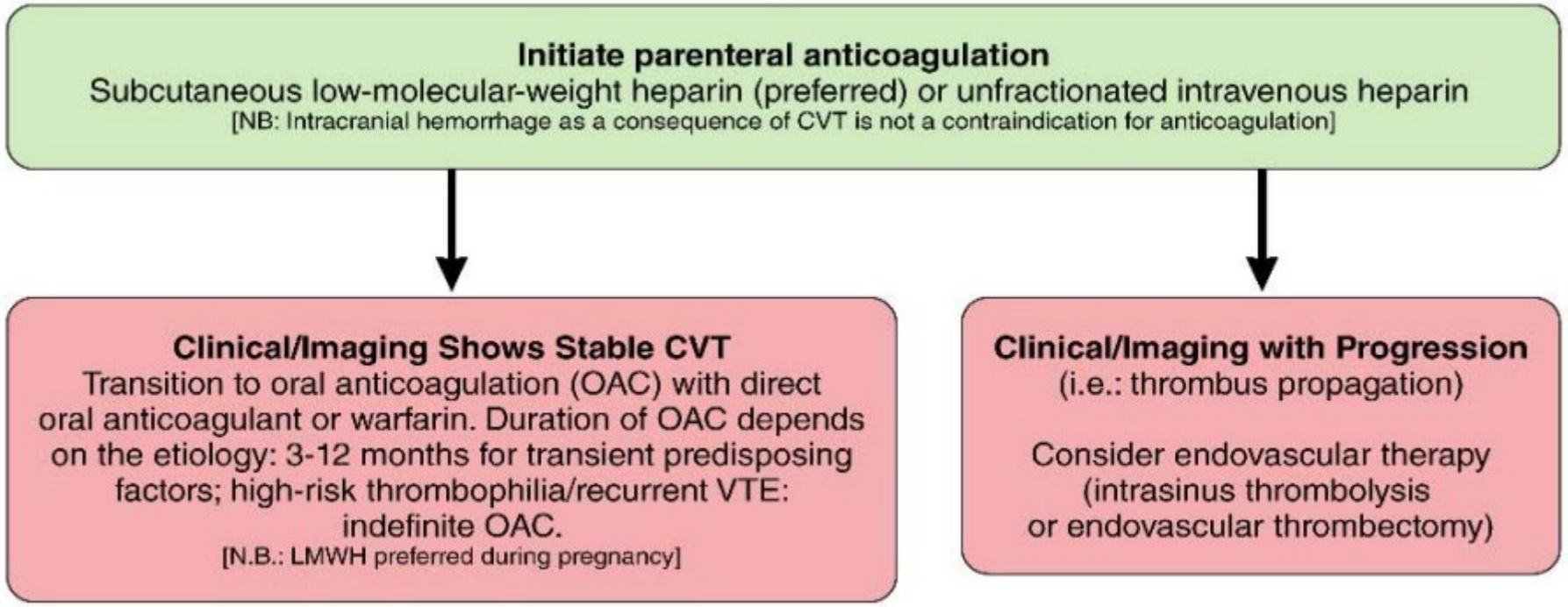
THERAPEUTIC ADVANCES IN THE MANAGEMENT OF CVT - OVERVIEW



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CEREBRAL VENOUS THROMBOSIS IN SPECIAL POPULATIONS

CEREBRAL VENOUS THROMBOSIS IN SPECIAL POPULATIONS - PEDIATRIC

- CVT is more common in neonates (6.4/100,000) than in children or adolescents
- CVT needs to be considered early in acute presentations of headache, seizures, focal neurologic deficits, coma, head trauma, hypoxia and/or dehydration
- Management of acute DVT typically involves low molecular weight or unfractionated heparin followed by oral therapy
  - Optimal duration of anticoagulation and preferred oral agent are unclear
- Long-term studies suggest that one in four children despite treatment may develop
  - Late epilepsy
  - Infantile spasms post-neonatal CVT
  - Cognitive impairment
  - Intracranial hypertension

CEREBRAL VENOUS THROMBOSIS IN SPECIAL POPULATIONS – PREGNANCY AND PUERPERIUM

- CVT incident estimates during pregnancy and puerperium range from 1 in 2,500 deliveries to 1 in 10,000 deliveries in Western countries with ORs ranging from 1.3 to 13.0
- Period of greatest risk is third trimester and the first 6 weeks postpartum with 80% occurring after delivery
- Cesarean delivery associated with higher risk (OR 3.1)
- Prognosis of pregnancy-related CVT similar and maybe better than CVT patients in general
- Low molecular weight heparin is agent of choice during pregnancy and early in the puerperium
  - Vitamin K antagonists associated with fetal embryopathy and bleeding in the fetus and neonate and are contraindicated
  - DOACs are contraindicated during pregnancy and while breastfeeding
- Future pregnancy is not contraindicated though prophylaxis with low molecular weight heparin is usually recommended

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CEREBRAL VENOUS THROMBOSIS IN SPECIAL POPULATIONS – VACCINE INDUCTED THROMBOTIC THROMBOCYTOPENIA

- CVT and thrombocytopenia reported following vaccination for COVID infection
  - Headache the most common presenting feature
  - All patients had thrombocytopenia
  - Some patients found to have antibodies to platelet factor 4 (PF4)
  - Risk lower after mRNA SARS-CoV-2 vaccines compared to adenovirus-based SARS-CoV-2 vaccines (1-5/10,000 vs 13/10,000)
- CVT is rare but carries poor prognosis with mortality rates ranging from 39-61%
- In cases of suspected vaccine induced thrombotic thrombocytopenia recommendations include:
  - Testing for PF4
  - Avoidance of heparin products (consider argatroban, fondaparinux, etc.)
  - Administration of intravenous immunoglobulin 1g/kg body weight daily for 2 days
  - Administration of steroids
  - Transition to oral anticoagulant once there is full platelet count recovery

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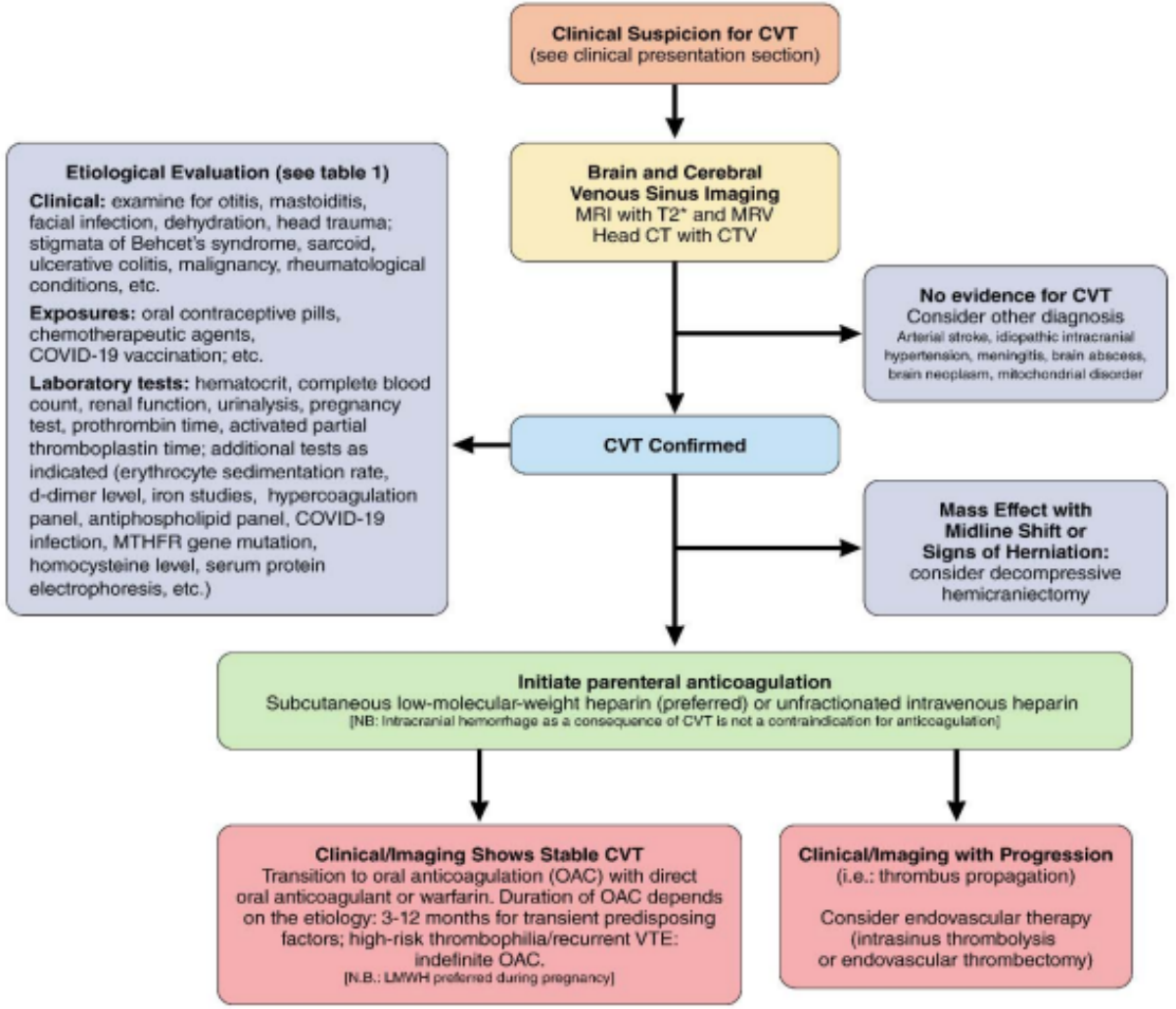
CEREBRAL VENOUS THROMBOSIS - OVERVIEW



Legend: This figure summarizes the suggested approach for the diagnosis and management of CVT.

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