



### OBJECTIVE:

To assist health care professionals in the management of cerebral venous thrombosis (CVT).

For information related to CVT in the context of Vaccine-induced Thrombotic Thrombocytopenia (VITT), please consult **Clinical Guide Vaccine-induced Prothrombotic Immune Thrombocytopenia (VIPIT/VITT)**.

### BACKGROUND:

The cerebral venous system is comprised of the dural venous sinuses, deep and cortical cerebral veins, cavernous sinuses, and internal jugular veins. CVT refers to thrombosis affecting any of these sites. CVT is rare, with an incidence of approximately 10-20 per million person-years and accounting for approximately 1% of all strokes.

In contrast with pulmonary embolism (PE) and deep vein thrombosis (DVT), CVT primarily affects younger individuals, with approximately 80% of cases occurring in individuals under the age of 55. Women are predominantly affected, with 75% of cases affecting females, and over 50% of cases associated with oral contraceptive use or the puerperium. However, these sex differences attenuate after the age of 50.

The presenting symptoms associated with CVT can be secondary to increased intracranial pressure (ICP; headache, nausea, vomiting, blurred vision, diplopia), parenchymal injury secondary to edema or hemorrhage (focal deficits, decreased level of consciousness or encephalopathy), or cortical irritation (seizures). The most common presenting symptom is headache (90%), with seizures occurring in approximately 40% and focal deficits in 20-40%. Approximately 30% of individuals will present with some amount of intracranial bleeding secondary to parenchymal injury. Intracerebral blood is most common, with subarachnoid or subdural blood less frequently.

General risk factors for CVT include hormonal therapy, pregnancy, heritable and acquired thrombophilias, malignancy (especially hematologic malignancies), systemic infections, collagen vascular diseases, including vasculitic disorders (e.g. systemic lupus erythematosus, granulomatosis with polyangiitis, and Behcet's disease) and inflammatory bowel disease. Local risk factors include head trauma, neurosurgery, spinal procedures, and head and neck infection (e.g. meningitis, otitis, mastoiditis). In less than one quarter of cases, no apparent cause is found.

While most CVT survivors (approximately 85%) will be functionally independent following their event, 5-10% will die, and over half may experience persisting issues related to headache, fatigue, mood or cognition affecting quality of life. Longer-term prognostic data on VTE recurrence is limited. The existing literature suggests that risk of any recurrent VTE is approximately 2-4% per year, with higher rates of recurrence in those with identified thrombophilia, malignancy, and unprovoked events.

## **DIAGNOSIS OF CEREBRAL VENOUS THROMBOSIS:**

In most cases, non-contrast CT head is not sufficiently sensitive to diagnose CVT. CT venography or contrast-enhanced MR venography should be performed in individuals being assessed for possible CVT. Imaging with non-contrast CT or MRI will help to assess for the presence of parenchymal injury, including venous edema, intracranial bleeding, and signs of mass effect.

## **MANAGEMENT OF CEREBRAL VENOUS THROMBOSIS:**

Given the uncommon nature of CVT, recommendations are based on limited randomized data and observational cohort studies. The primary purpose of treatment is to prevent secondary brain injury and mortality from venous infarction, intracerebral hemorrhage or malignant (ie. life-threatening) mass effect. The general management approach consists of: 1) anticoagulant therapy, 2) management of increased ICP, 3) seizures and 4) headache.

Some patients with CVT may be at risk of neurological deterioration with depressed level of consciousness or new onset of focal deficits due to intracranial bleeding, increased ICP or seizures. Therefore, the need for initial management in an intensive care/high-acuity setting should be assessed early, with recommended early involvement of Neurology and Hematology/Thrombosis services.

### **Anticoagulant therapy**

Anticoagulation, even in the presence of intracranial blood, is the standard-of-care treatment for CVT. Unlike primary intracerebral hemorrhage, the mechanism of intracranial bleeding in CVT is usually due to increased venous pressure, therefore improvement of venous obstruction generally reduces the impetus for bleeding. There may be rare cases where there are concerns regarding the safety of anticoagulation (e.g. large or rapidly expanding intracranial hemorrhage, anticipated emergent surgical decompression) that will require case-by-case collaborative decision-making by neurology and hematology/thrombosis.

Usually, either parenteral anticoagulation with unfractionated heparin (UFH) or low-molecular weight heparin (LMWH) is initiated, with subsequent transition to oral anticoagulation once the patient is stable (see “duration of therapy” for considerations regarding longer-term anticoagulation). In patients not forecasted to require early neurosurgical intervention or those deemed to not have a high risk of life-threatening bleeding we favour the use of LMWH over UFH for a more reliable quality of anticoagulation.

Current guideline-recommended oral anticoagulation is with a Vitamin K antagonist (VKA) with INR target 2.0-3.0. However, the recent RESPECT-CVT trial, (published subsequent to the most recent guideline updates from the American Heart Association/American Stroke Association and the European Stroke Organization) found no differences in rates of major bleeding (one GI bleed in the dabigatran arm, 2 ICH in the warfarin arm) or venous recanalization between dose-adjusted warfarin and dabigatran 150 mg bid, initiated 5-14 days after parenteral anticoagulation and continued for 6 months. The trial, which enrolled 120 participants, was exploratory and not powered for efficacy or safety outcomes. A substudy of the EINSTEIN-Jr trial examined use of rivaroxaban for CVT in 114

children. The trial randomized children with VTE after 5-9 days of parenteral anticoagulation 2:1 to three months of rivaroxaban 20 mg-equivalent dosing versus vitamin K antagonist or parenteral anticoagulation. There was one recurrent VTE in the standard therapy group and one major bleeding event (ICH), whereas in the rivaroxaban arm there were 5 clinically relevant non-major bleeding events with no VTE recurrence and no major hemorrhage. There are other ongoing trials currently investigating DOACs for CVT (Clinicaltrials.gov – NCT03178864, NCT03191305, NCT03217448, NCT03747081), which will contribute additional information to inform the use of these agents in CVT.

### *Deterioration despite anticoagulation*

Some patients may deteriorate despite use of anticoagulation, either due to mass effect (secondary to venous infarction and/or hemorrhage) or thrombus extension. In cases of life-threatening mass effect, urgent neurosurgical consultation is warranted for decompressive hemicraniectomy.

Mechanical thrombectomy may be appropriate in cases where neurological deterioration is secondary to thrombus extension. Interdisciplinary collaboration may be required to determine what the best course of action may be for severe cases. The TO-ACT trial examined routine use of neurointervention (endovascular therapy, intradural thrombolytic or both as per local practice) versus conservative management in patients with severe CVT (decreased level of consciousness or mental status disorder, intracranial bleeding, and/or deep venous involvement). The trial, which was terminated early for futility after 67 patients of a target of 164 were recruited, found no difference in the rates of favourable neurological outcome at 12 months. Three of 33 interventional patients experienced intraprocedural venous sinus perforation. Thus routine use of neurointervention is not recommended, with case-by-case decision making as needed for severe presentations.

### **Management of increased intracranial pressure (ICP)**

Increased intracranial pressure is commonly seen in CVT. In individuals with ICP associated with optic nerve changes (papilledema, enlarged blind spots or other visual loss) or diplopia, acetazolamide may be considered alongside involvement of the ophthalmology service for monitoring.

Acetazolamide may also be considered for management of intracranial hypertension without visual changes on a case-by-case basis, in addition to conservative measures such as head of bed elevated to 30 degrees or above.

Surgical treatment such as shunting or optic nerve fenestration may be warranted in refractory cases, or in cases where the consequence of CVT results in significant hemorrhage and mass effect requiring neurosurgical intervention.

### **Seizure management**

Approximately 30-40% of patients with CVT will experience seizures, with over 10% experiencing seizures after the acute stage. Referral to a neurologist is indicated. Clinicians should be aware of the

drug-drug interactions that exist between several common antiseizure medications and oral anticoagulants (both vitamin K antagonists as well as DOACs).

There is no evidence supporting the use of prophylactic antiseizure therapy in those without seizures.

## **Headache**

Approximately 90% of patients with cerebral venous thrombosis will present with headache, which may be severe in some cases. Appropriate analgesia is important both for patient comfort in addition to the fact that severe pain and vomiting can contribute to increased ICP. While headache generally improves with initiation of therapy for CVT and ICP management, some may have ongoing chronic headache that may impact quality of life. Referral for ongoing pain management in the outpatient setting is indicated in these cases.

## **Risk factor management**

- Provoking factors, including hormonal therapies, should be discontinued. Lifestyle modifications including smoking cessation should also be encouraged.
- Heritable and acquired thrombophilias are risk factors for CVT although the implications for choice and duration of anticoagulation therapy are uncertain in most cases. Routine testing is thus not currently recommended.
- In patients with a known history of antiphospholipid antibody syndrome (APLAS), use of DOACs is not recommended. The TRAPS trial, which randomized individuals with triple-antibody-positive APLAS and a history of arterial or venous thromboembolism to a switch to rivaroxaban versus continuing Vitamin K antagonist anticoagulation, was stopped early due to an excess of recurrent arterial thromboembolic events in the rivaroxaban arm. Other trials investigating DOACs in lower-risk individuals with APLAS are ongoing ([clinicaltrials.gov NCT02295475](https://clinicaltrials.gov/ct2/show/study/NCT02295475)).

## **DURATION OF THERAPY:**

- The optimal duration of anticoagulation in CVT has not been established. As mentioned, the observational data on longer-term recurrence is limited but risk of recurrence in those without an indication for permanent anticoagulation appears to be higher in men, in individuals with inherited thrombophilias and in those with cryptogenic events. Recommendations for duration have been extrapolated from data for DVT and PE and should be based on the patient's individual circumstances.
- CVT in the context of a reversible provoking factor should generally be treated for 3-6 months. In individuals in whom CVT was unprovoked, at least 6-12 months of anticoagulation is suggested. Individuals who have recurrent CVT, prior venous thromboembolism or in whom there is an ongoing provoking factor should be considered for extended anticoagulant therapy with periodic reassessment for bleeding risk, as should those without high risk features for bleeding but are uncomfortable with estimated risks of recurrence associated with anticoagulant discontinuation.

- Data about the risk of CVT during a subsequent pregnancy and the impact of thrombosis prophylaxis on that risk are limited. Systematic review data suggests that in women with a history of CVT the relative risk of non-cerebral VTE is 16-fold and risk of recurrent CVT 80-fold than the baseline risk in the general population. In the absence of robust data, it is reasonable to prescribe antepartum and postpartum prophylaxis to pregnant women with a prior history of CVT and no contraindication for anticoagulation.

#### **OTHER RELEVANT THROMBOSIS CANADA CLINICAL GUIDES:**

- Dabigatran (Pradaxa®)
- Deep Vein Thrombosis (DVT): Treatment
- Pulmonary Embolism (PE): Treatment
- Unfractionated Heparin, Low Molecular Weight Heparin, and Fondaparinux
- Vaccine-induced Prothrombotic Immune Thrombocytopenia (VIPIT/VITT)
- Venous Thromboembolism: Duration of Treatment
- Warfarin

*\*Note on terminology and pathophysiology - Intracranial bleeding refers to any bleeding within the skull (ie. intracerebral hemorrhage, subdural bleeding, subarachnoid bleeding), whereas intracerebral hemorrhage refers specifically to intraparenchymal and/or intraventricular brain bleeding. Any of these may lead to increased intracranial pressure, either due to focal mass effect or obstruction of csf circulation (hydrocephalus).*

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