

# Critical care management of cerebral venous thrombosis

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## Purpose of review

Although recent trials of intervention for acute ischemic stroke have been positive, similar benefit in acute cerebral venous thrombosis (CVT) remains largely unclear. This review aims to summarize the existing evidence regarding the management of CVT, including anticoagulation and endovascular therapy.

## Recent findings

The mainstay of treatment in CVT is systemic anticoagulation even in the setting of intracerebral hemorrhage. Nonrandomized studies and case series suggest that endovascular therapy in CVT is relatively safe, and can improve outcomes in the small subset of CVT patients with neurologic deterioration despite anticoagulation.

## Summary

Despite a generally favorable prognosis, one in four patients with CVT develop neurological deterioration in the acute phase. Predisposing factors include a neurological deficit or seizures at onset, deep venous thrombosis, venous infarctions, or intracranial hemorrhage with mass effect and an underlying thrombophilia. More randomized trials are needed to compare the benefits of anticoagulation and endovascular therapy.

## Keywords

anticoagulation, cerebral venous thrombosis, endovascular, thrombectomy, thrombolysis

## INTRODUCTION

Cerebral venous thrombosis (CVT) is a relatively rare cause of stroke, accounting for only 0.5 to 1% of all acute strokes [1]. It typically presents with new onset of persistent headache or as a syndrome of increased intracranial pressure (ICP). Approximately, one-third of patients may develop seizures, whereas others may develop a focal neurologic deficit or encephalopathy. A variety of underlying risk factors can promote CVT, including prothrombotic states (both acquired and inherited), drugs, such as oral contraceptives, pregnancy and the puerperium, malignancy, infection, mechanical factors, and miscellaneous conditions. In the largest multinational multicenter prospective cohort study on CVT to date, the International Study on Cerebral Vein and Dural Sinus Thrombosis (ISCVT), the two most common risk factors were an underlying thrombophilia (34%) or the exposure to oral contraceptives (54%) [2]. At least one risk factor was identified in 85% of cases, and two or more in 44% of patients [2].

## DIAGNOSIS

The diagnosis of CVT is based on dedicated venous neuroimaging with computed tomography venography (CTV) or magnetic resonance venography (MRV). The diagnosis is confirmed by evidence of a filling defect in the venous system (Fig. 1). Additional findings suggestive of CVT include cerebral edema, lobar ICH, and bilateral or atypical strokes not respecting arterial territories. The most commonly involved sinuses are the superior sagittal (62%), transverse-sigmoid (41–45%), straight

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**KEY POINTS**

- One in four patients develop neurological deterioration.
- Acute complications of CVT include ischemic stroke and ICH, ICP, hydrocephalus, and seizures.
- Anticoagulation with LMWH or UFH is recommended in the acute phase and well tolerated even in the presence of ICH.
- Endovascular therapy, including systemic and i.v. thrombolytics and mechanical thrombectomy, can be used in the acute setting in patients with neurologic deterioration despite anticoagulation therapy or when anticoagulation is contraindicated (other than ICH due to CVT).
- Low GCS, altered mental status, posterior fossa lesions, right ICH, and thrombosis of deep veins are predictors of mortality in the acute phase.

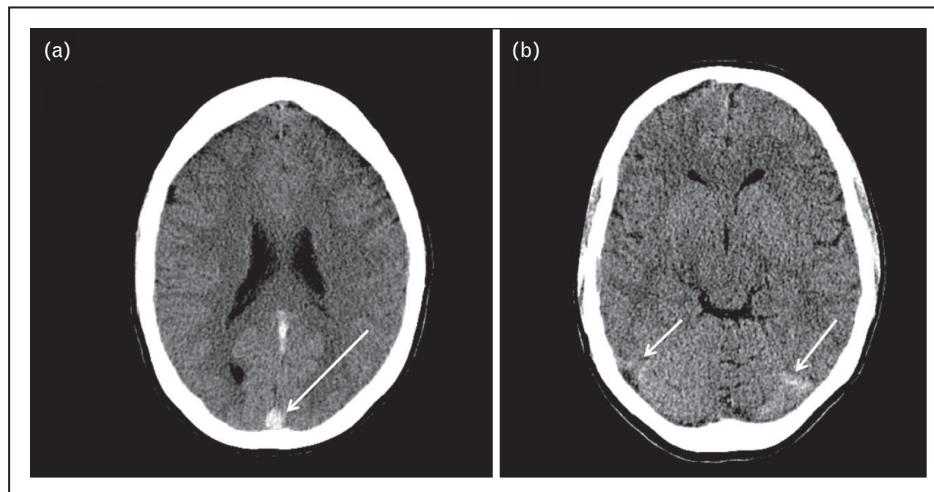
sinus (18%), jugular vein (12%), and deep venous system (11%) (Fig. 2). An MRI/MRV has been recommended by the American Heart Association (AHA) and European Federation of Neurological Societies (EFNS), as a negative CTV does not rule out the possibility of CVT. Cerebral angiography is reserved for complex cases despite negative neuroimaging or when CTV or MRV are not available. Repeat imaging with CTV/MRV is also recommended in patients with persistent, worsening, or recurrent symptoms of CVT despite treatment and at 3–6 months to check for recanalization in stable patients [3].

**MANAGEMENT OF CEREBRAL VENOUS THROMBOSIS****Acute antithrombotic treatment****Initial anticoagulation**

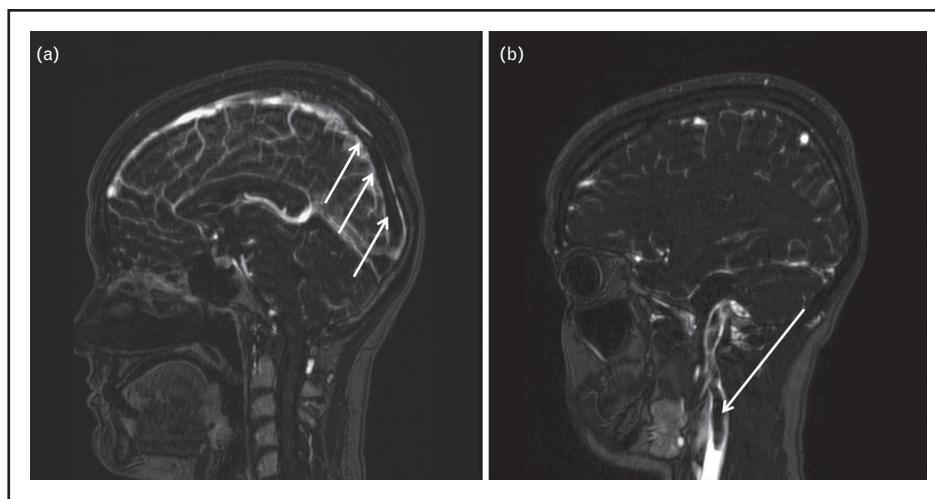
The mainstay of therapy for CVT is anticoagulation. The goals of treatment include prevention of sinus thrombus extension, sinus recanalization, and prevention of systemic venous thromboembolism [3].

Two randomized controlled trials have compared heparin with placebo in CVT. They comprise a combined sample size of only 79 patients. The first trial included 20 patients, 10 randomized to dose-adjusted intravenous (i.v.) heparin and 10 to placebo. The primary end point was clinical outcome on a CVT severity scale. Enrollment in the trial was stopped early after detection of a significant improvement in the treatment group. At 3 months, eight of the 10 patients receiving anticoagulation experienced complete neurologic recovery vs. only one in the control group. There was no evidence that heparin treatment promoted ICH [4].

The second trial comprising 59 patients with CVT compared subcutaneous nadroparin with placebo for 3 weeks. The primary end point was defined as poor outcome or death at 3 weeks. There was a nonsignificant trend toward a better outcome in the treatment group. In total, six (10%) patients died. All of the deaths occurred in the subgroup with baseline cerebral hemorrhage on CT, but there was no evidence to suggest cerebral hemorrhage was worsened by anticoagulation [5].



**FIGURE 1.** Unenhanced computed tomography brain showing hyperdensity at the confluence of the sinuses (arrow) (a). There are bilateral linear hyperdensities in the parietal lobes (arrows) corresponding to thrombosis of cortical veins (b).



**FIGURE 2.** Magnetic resonance venogram showing long linear filling defect in the superior sagittal sinus (arrow) (a) and right internal jugular vein (arrow) (b).

A subsequent meta-analysis of these studies found that anticoagulation was associated with a nonsignificantly decreased risk of death or dependency. Use of anticoagulation in CVT was deemed to be safe, including low risk of ICH [5,6].

Regarding choice of anticoagulant, there is limited evidence to support choosing low-molecular-weight heparin (LMWH) over unfractionated heparin (UFH). An open-label randomized trial assigned 66 patients to treatment with either UFH or LMWH for 14 days followed by oral anticoagulation. Hospital mortality was significantly reduced in the group treated with LMWH. The mortality benefit may be associated with the longer duration of action and more stable therapeutic action of LMWH. There was no difference in outcome at 3 months between the groups [7]. Additional benefits of LMWH include easier route of administration and no requirement for regular laboratory monitoring. One benefit of UFH is rapid normalization of activated partial thromboplastin time (1–2 h) following cessation, should complications of anticoagulation arise or if emergency surgical intervention is needed [8].

In a study analyzing the original ISCVT cohort, 302 patients received UFH alone vs. 119 who received only LMWH. More patients were independent at 6 months in the LMWH group vs. UFH (92 vs. 84%, odds ratio 2.4, confidence interval 1.0 to 5.7,  $P=0.04$ ). There was also a nonsignificant decrease in new ICH and overall mortality in the LMWH group [9].

The EFNS guidelines recommend that patients without contraindication for anticoagulation should be treated with either weight-adjusted subcutaneous LMWH or dose-adjusted i.v. UFH, aiming

for activated partial thromboplastin time twice the upper limit of normal [8]. This recommendation is similar to the 2011 AHA/ASA guidelines [3]. Both guidelines state that ICH is not a contraindication for anticoagulation [3,8].

The AHA guidelines advocate a similar approach in children beyond 28 days of life, with the use of either UFH or LMWH, even in cases of secondary hemorrhage [10]. The treatment of neonates is more controversial, with a paucity of data. There is no general consensus on whether to initiate treatment. This partly stems from initial concerns over the susceptibility of the neonatal brain to hemorrhage (and different underlying causes/predisposing factors). Case studies and an observational case series suggest that neonatal CVT treated with anticoagulation appears to have good outcomes, even in the presence of hemorrhage, whereas neonatal CVT not receiving anticoagulation resulted in a higher rate of thrombus propagation [3,11,12]. The 2011 AHA guidelines state that treatment with LMWH for 6 weeks to 3 months may be considered in neonates [3].

Finally, the majority of pregnant women with CVT should be treated with anticoagulation. The 2011 AHA guidelines echo the 2008 American College of Chest Physicians recommendation for the use of full-dose anticoagulation with LMWH over UFH for lower risk of teratogenicity. Treatment should be continued for at least 6 weeks postpartum [13], but warfarin should be avoided because of its known teratogenicity.

There are currently no controlled trials or observational studies assessing the use of aspirin or anti-platelet agents in CVT [3].

## Endovascular treatment

Endovascular intervention is an alternative strategy in the subset of patients who deteriorate neurologically despite adequate medical management. The options include intravascular administration of thrombolytics, mechanical thrombectomy, and combination treatment. There is currently no high-quality evidence to support the use of endovascular therapy as the initial approach with evidence limited to isolated case reports or uncontrolled case series. The ongoing Thrombolysis or Anticoagulation for Cerebral Venous Thrombosis (TO-ACT) trial is the first randomized trial comparing endovascular therapy with standard anticoagulation therapy [14]. Overall, 54 patients have been randomized. Final results are expected by December 2016.

## Endovascular thrombolysis

A systematic review of thrombolysis for CVT included 169 patients from a large number of studies ( $n=72$ ) [15]. Most patients had a poor baseline neurologic status, including 78% with encephalopathy and coma. Patients received intracerebral or systemic thrombolysis, either alone or in combination. Overall, 86% of patients were independent at discharge. Death occurred in 5% of patients, with an additional 7% who remained dependent at discharge.

## Mechanical thrombectomy

Borhani and colleagues [16] provided a comprehensive literature review of 64 mechanical thrombectomy procedures for patients with CVT between 1990 and 2012. Overall, 62.5% had no disability or minor disability, whereas mortality occurred in 16.1% of participants [16]. Another recent review [17<sup>\*</sup>] analyzing mechanical thrombectomy in CVT evaluated 42 studies comprising 185 patients. A large proportion of patients had initially poor neurologic status (47% in coma). Seventy-one percent of patients received concurrent intravascular thrombolysis. A good outcome, defined as modified Rankin Scale (MRS) score of 0–2 was reported in 84% of cases. Death occurred in 12% of patients. New or increased periprocedural intracranial hemorrhage was identified in 10% of cases [17<sup>\*</sup>].

The data suggest that endovascular therapy may reduce mortality in CVT patients with decreased level of consciousness. The caveat is that there may be publication bias from over inclusion of cases with good outcomes [2,18]. Accordingly, the AHA guidelines recommend consideration of endovascular intervention in cases where deterioration occurs despite intensive anticoagulation [3]. At present, it is difficult to draw any definitive conclusions

regarding endovascular therapy in CVT without high-quality data from randomized controlled trials.

## Acute symptomatic treatment

### Elevated intracranial pressure and hydrocephalus

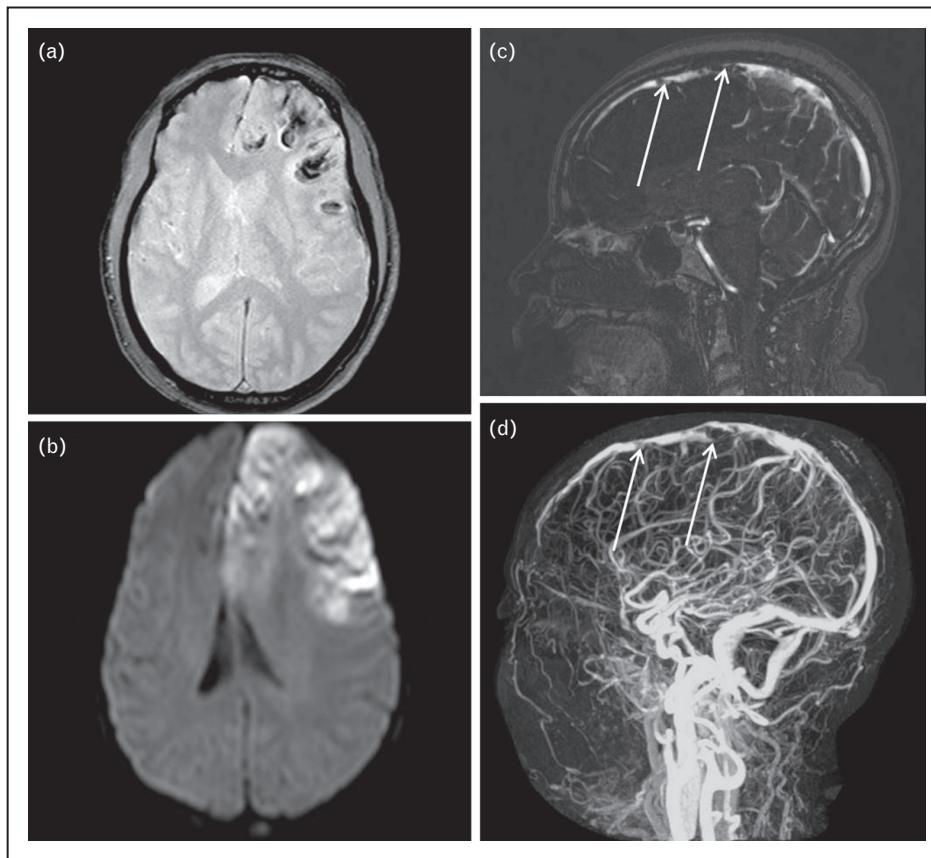
High ICP leading to transtentorial herniation is the most common cause of death acutely in CVT [2]. The combination of blockage of venous outflow and cerebrospinal fluid malabsorption can result in single or multiple infarcts, hemorrhages, or brain edema. Additionally, blockage of arachnoid granulations and ventricular extension of hemorrhage can result in both communicating and noncommunicating hydrocephalus. Clinically, patients may present with headache, visual disturbance, seizures, or false localizing cranial nerve deficits.

There are no randomized clinical trials comparing methods used to treat high ICP in CVT. Treatment with anticoagulants or thrombolytics may lessen clot burden and reduce ICP. General supportive measures to acutely lower ICP include elevating the head of the bed, hyperventilation to lower partial pressure of carbon dioxide in arterial blood between 30 and 35 mmHg, mannitol, acetazolamide, or other diuretics. Another option is high-volume or serial lumbar puncture, although there may be added risk of bleeding associated with concomitant anticoagulation. Patients with hydrocephalus refractory to treatment may require an external ventricular drain or shunting [3].

There is currently no evidence to support the use of steroids for increased ICP in CVT. In the ISCVT, 150 patients received steroids, but there was no significant difference in the primary or secondary outcomes among patients receiving and not receiving them. Furthermore, there is some evidence that steroids may cause harm in those with high ICP without parenchymal lesions [19].

### Decompressive hemicraniectomy

Previous randomized controlled trials investigating decompressive hemicraniectomy in malignant middle cerebral artery stroke found a reduction in mortality and poor outcomes in patients age 60 or younger treated with decompressive hemicraniectomy within 48 h [20]. Decompressive hemicraniectomy can be considered in cases of imminent transtentorial herniation. One study with a retrospective design and a systematic review identified 69 patients treated with decompressive hemicraniectomy for CVT. A good outcome (MRS 0–2) was observed in approximately 39 (56.5%) patients.



**FIGURE 3.** A 37-year-old woman who died during the acute stage of cerebral venous thrombosis. There is a large left frontal infarct on diffusion-weighted imaging (a) with hemorrhagic components on gradient echo (b). The infarct does not correspond to a single arterial territory. There is notable mass effect and midline shift. There are filling defects (arrows) in the superior sagittal sinus (c and d).

### Seizures and seizure prophylaxis

Seizures on presentation occur in approximately 37% of adults and 48% of children [3]. Factors predicting presenting seizure in the ISCVT were supratentorial lesion, cortical vein thrombosis, superior sagittal sinus thrombosis, and puerperal thrombosis. Supratentorial lesions and presenting seizure were increased risk factors for early seizure (seizure within 2 weeks of CVT diagnosis). The risk of early seizures in the highest risk group – those with supratentorial lesions and presenting seizure – was significantly lower with the use of antiepileptic drug (AED) prophylaxis. In patients without supratentorial lesion, risk of recurrent seizure was low regardless of presenting seizure, occurring in only one patient vs. 0 on AED prophylaxis [21].

There are no randomized trials investigating AED prophylaxis in CVT. A Cochrane review found insufficient evidence to support or refute the use of AED for primary or secondary prevention of seizure in CVT [22]. The current recommendation from the AHA is the use of AED prophylaxis in

patients with parenchymal lesions and seizure on presentation. Seizure prophylaxis is not recommended in patients who do not have seizures [3].

The EFNS guidelines deem it reasonable to continue AED in patients with both early seizure and ICH on admission [8]. A more recent recommendation suggests that antiepileptic medications can be tapered off after 3–6 months if no further seizures occur [23\*].

### MANAGEMENT OF LATE COMPLICATIONS

#### Headache

Headache may persist in up to 50% of CVT patients [3,24,25]. One study with 55 CVT patients found persistent headache in 29 patients, although the vast majority (93%) was then diagnosed as migraine and tension headache [24]. Severe headache following the acute period may occur in 11–14% of patients [2,3,26]. Very rarely these headaches represent recurrent venous sinus thrombosis. Persistent or severe

headache should be investigated appropriately with MRV. If MRV is negative, a lumbar puncture may be warranted to exclude high ICP [3].

### Visual loss

Visual loss at presentation occurred in 13.2% of patients in the ISCVT [2]. Despite this, long-term severe visual loss in CVT occurs in only 2–4% of cases [3]. In patients complaining of visual disturbance or those with documented papilledema, visual acuities should be documented and formal visual fields should be obtained. Optic nerve fenestration can be considered as a therapeutic option in patients with persistent or progressing symptoms [3].

### Prognosis

#### Early deterioration and death

Early death occurs in approximately 5% of patients, ranging between 0 and 15% [2,27–29]. In the ISCVT, predictors of mortality within 30 days of symptom onset include Glasgow Coma Scale (GCS) score less than 9, mental status disturbance, seizure, thrombosis of deep veins, right hemisphere hemorrhage, and posterior fossa lesions [2]. The main cause of death in the acute phase is transtentorial herniation resulting directly from CVT (Fig. 3). Approximately, one in four patients will experience neurologic worsening from the time of diagnosis [27]. This can manifest clinically in a number of ways, including worsening level of consciousness, seizure, new or worsening preexisting focal neurologic deficit, worsening headache, or visual loss. An estimated one-third of these patients will have a new brain lesion on imaging [30].

#### Long-term outcome

Long-term outcome in CVT is generally favorable, with estimated 85–89% of patients achieving complete recovery or independence (MRS 0–2) [27,29]. Women have a more favorable prognosis than men entirely because of sex-specific risk factors (oral contraceptives, hormone replacement therapy, pregnancy, and puerperium). Risk factors for poor outcome include malignancy, thrombosis of the deep venous system, intracranial hemorrhage on admission CT/MRI, GCS score less than 9, mental status disturbance, age less than 37 years, and male sex.

In the ISCVT, 8.3% of patients died within 16 months. Causes of death outside of the acute phase were related to the underlying condition, including severe infection, underlying malignancy, and systemic thromboembolism [29].

### Recurrence and recanalization rates

Recurrence rates of CVT and venous thromboembolism in adults are generally low, between 2 and 4% [3,29], with similar rates in children [31]. Studies on recanalization rates are somewhat limited. One study of 33 patients with CVT evaluated recanalization at 4 and 12 months using MRV. The authors found that 15 patients had incomplete recanalization with no difference at 4 and 12 months [32]. A systematic review compiling data from five studies found that recanalization rates were roughly 85% with no difference between recanalization at 3 months and 1 year. Only 154 patients total were included, but this suggests that most recanalization takes place in the first few months [2,3,29]. A more recent study, including 102 patients with CVT, assessed recanalization rates at 3-month intervals using serial MRV. They found that 50% of patients had partial or complete recanalization at 64 days (2 months), and complete recanalization at 169 days (6 months). Age less than 50 years and superior sagittal sinus thrombosis were predictive of complete recanalization [33].

### CONCLUSION

CVT is an uncommon cause of acute stroke, but a high index of suspicion should be maintained in any patient with unexplained encephalopathy or headaches, headaches refractory to treatment or high ICP. Anticoagulation should be initiated even in patients of ICH. There are currently no randomized trials comparing standard anticoagulation with endovascular therapy. At present, endovascular therapy is reserved for patients with neurologic deterioration despite appropriate anticoagulation. Data from randomized controlled trials, including the ongoing TO-ACT trial, are required for more definitive conclusions regarding early use of endovascular therapy in CVT.

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### Conflicts of interest

*Dr. Saposnik provided an expert opinion in medico-legal cases of CVT. Dr Fam has no conflicts of interest.*

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