BMJ Best Practice

Cavernous sinus thrombosis

Straight to the point of care

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Summary

Cavernous sinus thrombosis (CST) is a thrombus formation within the cavernous sinus, which may be either septic or aseptic in origin. Infection can spread to the cavernous sinus either as an extension of thrombophlebitis or by septic emboli. The origin of aseptic cavernous sinus thrombosis is usually through trauma or a prothrombotic condition.

In the pre-antibiotic era, infections of the middle third of the face were responsible for the majority of cases. Currently, acute sinusitis is the most common predisposing condition.

Diagnosis is usually made through clinical evaluation together with imaging (computed tomography or magnetic resonance imaging).

In the acute presentation, one eye is typically affected first, followed by the second eye within 48 hours of symptom onset.

Must be differentiated from meningitis. Common early clinical features of both conditions include fever, headache, vomiting, and nuchal rigidity.

Antibiotics should be started immediately because they have the greatest effect on prognosis.

Definition

CST is the formation of thrombus (clot) within the cavernous sinus, which can either be septic or aseptic. Septic CST is a rapidly evolving thrombophlebitic process with an infectious origin (typically from the middle third of the face, sinuses, ears, teeth, or mouth), affecting the cavernous sinus and its structures. Aseptic CST is usually a thrombotic process that is a result of trauma, iatrogenic injuries, or prothrombotic conditions.

Epidemiology

Cavernous sinus thrombosis (CST) is a rare disease. Both the incidence and mortality declined markedly following the introduction of antibiotics.[2] [3] Several hundred cases have been reported in the literature since this time. The condition can occur at any age but typically affects children and young adults. CST accounts for 1% to 4% of cerebral venous and sinus thrombosis, which has an annual incidence of approximately 2 to 4 per million people per year.[4] [5] A male or female predominance is uncertain; though one review of 88 case reports in the literature suggests a 2:1 male to female prevalence.[6]

Etiology

Causes of septic cavernous sinus thrombosis (CST):

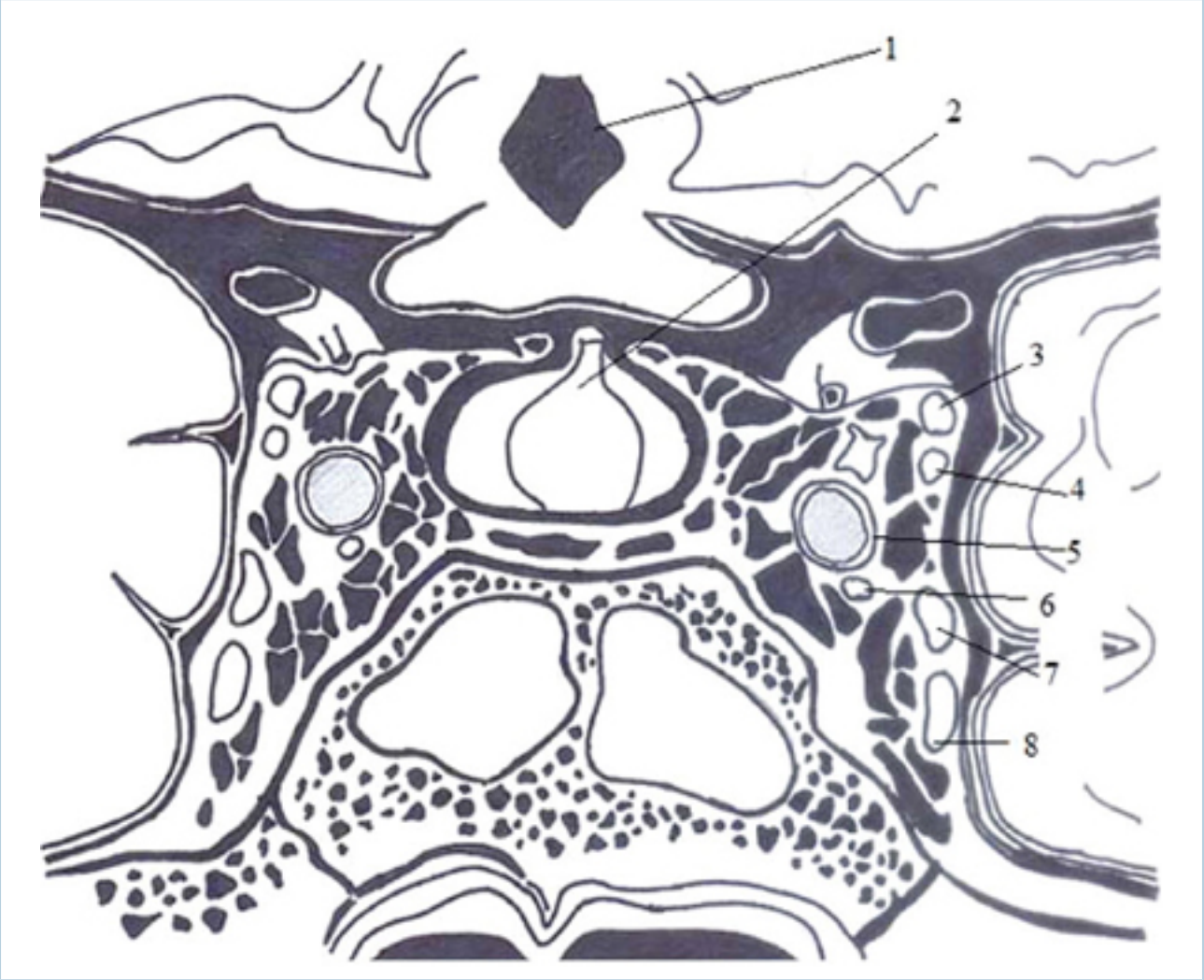
- Sinusitis: presently one of the most common predisposing conditions, representing an increase from 30% of all causes in the pre-antibiotic era.[2] [7] [8] [9] The most common site of primary infection is the sphenoid sinus, followed by the ethmoid sinuses.[10] [11] [12] [13] Infection is typically due to rare invasive and potentially resistant organisms. Early intervention improves prognosis.[12] [13] [14]
- Facial infection (e.g., folliculitis): in the pre-antibiotic era, this was the most common cause of CST, representing approximately 60% of cases.[15]
- Periorbital infection.
- Mucormycosis (highly invasive fungal infection, which usually occurs in immunocompromised patients, especially those with diabetes mellitus or neutropenia): may be either rhinocerebral or otocerebral.[16] [17]
- Otitis media and/or mastoiditis.[16] [18] [19]
- Petrous apicitis (infection of the medial portion of the temporal bone at the base of the skull).[20]
- Odontogenic infection.[15] [21] [22] [23]
- Bacterial meningitis.[24]
- Sepsis (other sources).
- Oropharyngeal infection resulting in Lemierre syndrome, which is a syndrome of septic thrombophlebitis of the veins of the head and neck.[25]

Causes of aseptic CST:

- Trauma (e.g., supraorbital, mandibular, or basilar skull fracture).[18] [22] [26]
- Postsurgical causes (e.g., rhinoplasty, cataract extraction, skull base procedures, and dental extraction).[27] [28] [29]
- Hypercoagulable state:
    - Owing to hematologic disorder (e.g., polycythemia rubra vera; sickle cell disease; acute lymphocytic leukemia; deficiencies of antithrombin III, protein C, or protein S; resistance to activated protein C; antiphospholipid antibody syndrome; thrombocytosis; elevated IgM).[22] [30] [31]
    - Owing to a nonhematologic disorder (e.g., nephrotic syndrome) or use of oral contraceptives.[32]
- Malignancy (e.g., rhabdomyosarcoma and nasopharyngeal carcinoma).
- Vascular abnormalities (e.g., carotid-cavernous fistula).[33]
- Miscellaneous etiologies (e.g., ulcerative colitis, volume depletion, or heroin overdose).[22] [34]
- Idiopathic.[35]

Pathophysiology

The cavernous sinuses are trabeculated venous channels extending anteriorly from the superior orbital fissure and posteriorly to the petrous portion of the temporal bone.



Anatomy of the cavernous sinus: (1) third ventricle, (2) pituitary gland, (3) oculomotor nerve, (4) trochlear nerve, (5) internal carotid artery, (6) abducens nerve, (7) ophthalmic branch of the trigeminal nerve, and (8) maxillary branch of the trigeminal nerve

Visvanathan V, et al. Reminder of important clinical lesson: ocular manifestations of cavernous sinus thrombosis. BMJ Case Rep. 2010; doi:10.1136. Used with permission

The cavernous sinuses are enclosed between the meningeal and periosteal layers of the dura. Coursing through the cavernous sinuses on each side are the internal carotid artery, cranial nerves III and IV (which lie in the lateral wall), the ophthalmic and maxillary branches of V (trigeminal nerve), and VI. These dural layers send trabeculae that give the sinuses a reticular pattern and can thereby trap bacteria, thrombi, or emboli. Bacteria also stimulate thrombogenesis by releasing toxins or by causing tissue damage.[35] Growth of the thrombus is thought to block antibiotic penetration in the cavernous sinuses. In that case, giving antibiotics will not be effective because the clot will prevent their penetration to the infected site where the bacteria are flourishing.[36] [37]

The cerebral emissary veins together with the dural sinuses are valveless and thus enable blood to flow bidirectionally in accordance with the pressure gradient in the vascular system.[1] Hence, infections that spread to the cavernous sinuses from the nose, sinuses, and middle third of the face travel in an anterograde direction to the cavernous sinuses, whereas dental, lateral venous sinus, and otogenic infections travel in a retrograde direction to affect the sinuses.[38]

The mechanism of pathogenesis can also be divided into 3 types:[2]

- Thrombophlebitis (vein inflammation related to a thrombus) with extension into the cavernous sinuses
- Embolization of infectious material, usually after trauma, abscess, or infection
- Phlebothrombosis (thrombosis of a vein without inflammation) or the aseptic form, which is differentiated from the other 2 by the absence of signs of sepsis or a primary source of infection.

Classification

Types of cavernous sinus thrombosis

Septic:

- Acute septic thrombosis: a thrombophlebitic process arising from a primary source of infection. Rapidly progressive signs and symptoms, typically involving both eyes within 48 hours.
- Subacute (sometimes termed chronic): similar to the acute form but with slower presentation and more subtle symptoms. Usually presents with isolated unilateral lateral gaze palsy.

Aseptic:

- A thrombotic process that occurs in patients with hypercoagulable states or secondary to trauma. Presents subacutely with few or no signs and symptoms of sepsis.

Case history

Case history #1

A 67-year-old man presents to the emergency department with fever, headache, and right-eye pain. He reports that his condition started 3 weeks ago when he had an upper respiratory infection. His headache has become worse in the past 48 hours, and he has started to have severe right-eye pain, with associated nausea and vomiting. Self-treatment with warm compressors provides little relief. Past medical history is positive for hypertension, type 2 diabetes mellitus, and osteoarthritis of the knees. On physical examination, he appears acutely ill, with a temperature of 102°F (39°C). His head and neck exam is notable for bilateral periorbital swelling, tense bilateral proptosis, and both internal (blunted papillary response to light) and external ophthalmoplegia. Nasal exam shows purulence above the inferior turbinates.

Case history #2

A 50-year-old woman presents to the emergency department with a history of right-eye swelling and double vision. On examination, she is afebrile but tachycardic. Her right eye is proptotic, swollen, and red. Her left eye is normal. Complete physical exam shows edema of both ankles. She is a smoker and

also reports that she has been diagnosed with a "kidney disorder". Past medical history is positive for antithrombin III deficiency secondary to proteinuria. Past surgical history is negative.

Other presentations

Loss of visual acuity is a possible feature occurring acutely or subacutely in less than 50% of people with cavernous sinus thrombosis (CST).[1] It may be due to papilledema, corneal ulceration secondary to proptosis and loss of the corneal reflex, occlusion of the internal carotid, ophthalmic or central retinal artery, orbital congestion or an embolic phenomenon. Seizure should raise suspicion of intracranial suppuration complicating septic CST. Visual changes in chronic, aseptic CST tend to present with slowly progressive eye symptoms (swelling, pain, proptosis and, ultimately, decreased vision) over a variable period of time (in the order of days to weeks).

Approach

Typically, the diagnosis is based on the recognition of systemic manifestations of sepsis, venous congestion of one or both orbits, and injury to the structures within and around the cavernous sinus.[50] An accurate interpretation of these clinical features should alert the clinician to the diagnosis and must be supplemented by imaging and laboratory studies. Presentation in children is similar to that in adults.

The clinical presentation can be:

- Acute (e.g., resulting from septic embolization)
- Subacute (e.g., resulting from phlebothrombosis occurring in aseptic cavernous sinus thrombosis [CST]).

The initial presentation can be:

- Local (with involvement of the cranial nerves)
- Systemic (from extension of the infection into adjacent tissues, causing meningitis, subdural empyema, or pituitary necrosis).

History

A history should include information about:

- The presence of any predisposing infection
- The timing of onset
- The progression of signs and symptoms.

Recent facial, ear, oral, and dental infections or manipulations or a history of maxillofacial surgery or trauma should be sought and may provide clues to a possible underlying primary infection. Risk factors associated strongly with septic CST include recent history of acute sinusitis, history of facial infection, or orbital infection.[40]

The timing of the onset of signs and symptoms of septic CST is variable. The majority of patients present acutely in a toxic state. Less commonly, presentation is more indolent, usually secondary to dental or ear infections. Those cases demonstrate features of septic CST sequentially over several days.[7]

Headache is reported in 50% to 90% of cases of CST.[4] It is the most common early symptom, preceding ocular manifestations, and is demonstrated in patients with sinusitis more frequently than in those with facial infections.[7] [15] [51] The location of headache may be suggestive. It is usually unilateral, located over the regions innervated by the ophthalmic and maxillary branches of cranial nerve V, involving the retro-orbital or frontal areas, with occasional radiation to the occipital region.[15]

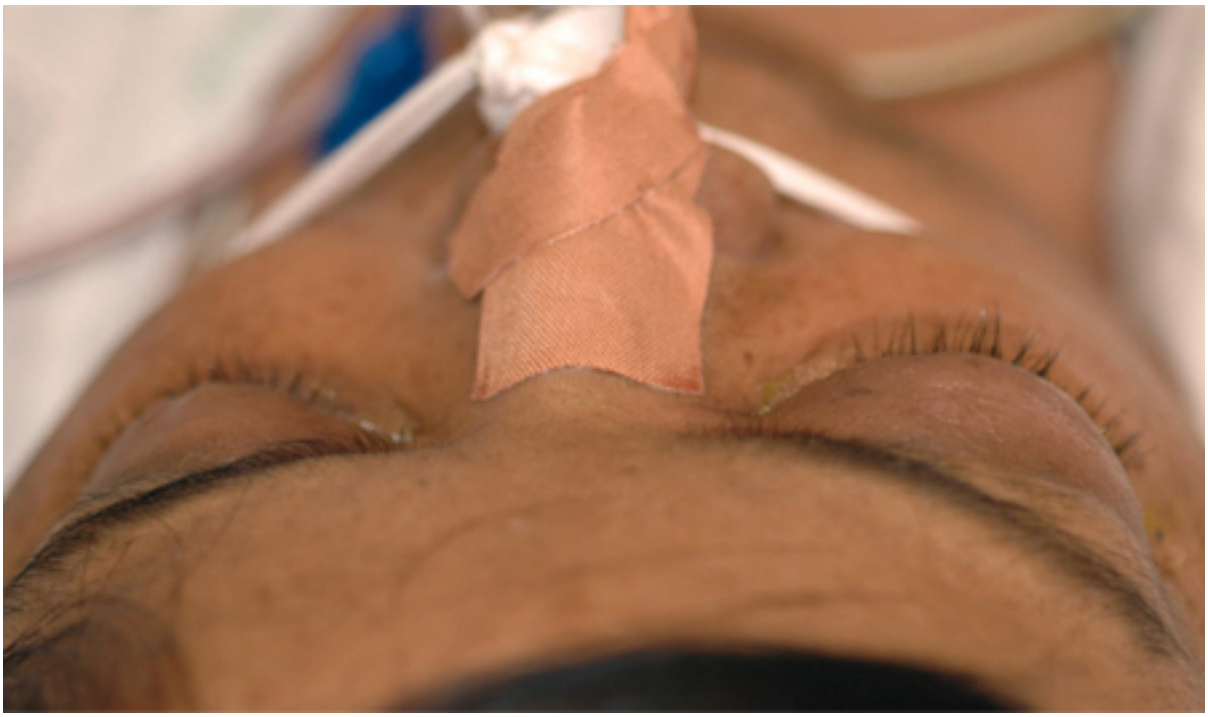
Fever occurs in almost all patients with septic CST and is usually severe.[41] Unilateral periorbital edema, spreading to the contralateral eye in the first 48 hours, is typically seen in septic CST.[4] [52] Extraocular muscle weakness, exhibited in almost all patients, usually follows chemosis and proptosis. Changes in mental status can develop rapidly, secondary to either central nervous system involvement or sepsis.

Patients with the aseptic form of the disease have a similar but more subtle presentation and do not demonstrate signs and symptoms of sepsis, meningitis, or primary infection. Risk factors strongly associated with the development of aseptic CST include a genetic prothrombotic condition or acquired prothrombotic state. The history should include inquiry about the presence of these factors, as well as

other associated features, such as a previous history of arterial or venous thrombosis, a history of cancer, or oral contraceptive use.

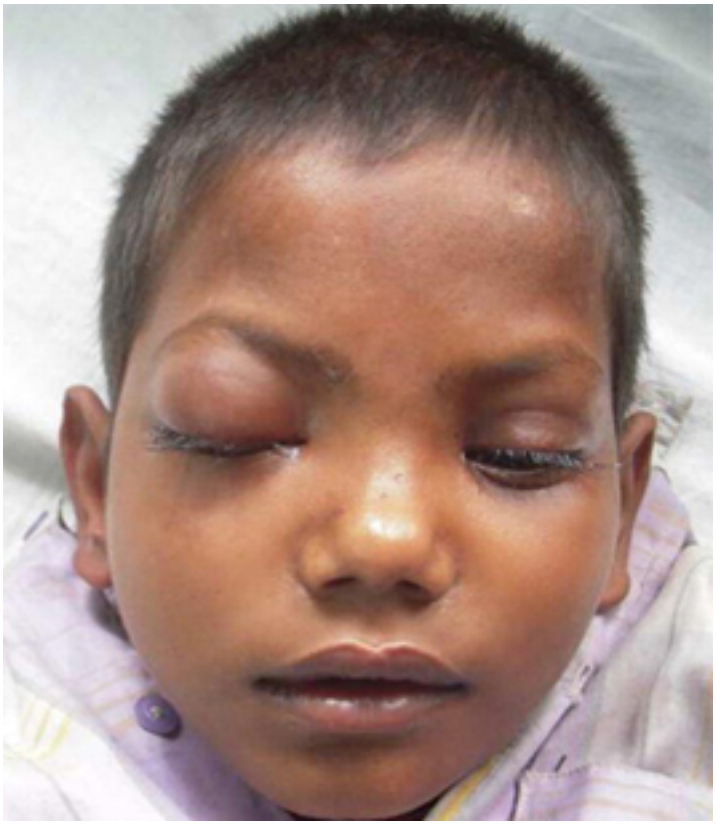
Physical examination

In the vast majority of patients, the physical findings of septic CST manifest rapidly.[41] The classic findings of fever, chemosis, proptosis, periorbital edema, and external ophthalmoplegia (restriction of extraocular muscles) are present in the majority of patients.



Proptosis of the right eye in a patient with cavernous sinus thrombosis secondary to dental infection

Jones RG, Arnold B. Sudden onset proptosis secondary to cavernous sinus thrombosis from underlying mandibular dental infection. BMJ Case Rep. 2009;2009. pii: bcr03.2009.1671. Used with permission



Patient with bilateral cavernous sinus thrombosis. Note the bilateral proptosis, which is more marked in the right eye

Vidhate MR, et al. Bilateral cavernous sinus syndrome and bilateral cerebral infarcts: a rare combination after wasp sting. J Neurol Sci. 2011;301:104-106. Used with permission

Ocular manifestatations of cavernous sinus thrombosis and their underlying pathology.

Anatomic region	Signs	Pathology/involved structure
Eyelids and Orbit	Ptosis	Edema of upper eye lid
		+/- sympathetic plexus
		involvement through III CN
	Chemosis	Thrombosis of superior & inferior ophthalmic veins
	Proptosis	
	Orbital cellulitis	
	Peri-orbital sensory loss	Involvement of V CN (ophthalmic/trigeminal divisions)
Cornea	↓Corneal reflex	V CN involvement (ophthalmic division)
	Corneal ulcers	Corneal exposure due to inability to close eyes.
Pupils	↓or absent Pupillary response	Raised intraocular pressure or optic neuropathy causing afferent pupillary defect
	Dialated	III CN (parasympathetic plexus)
	Small	sympathetic plexus involvement (III CN) affecting iris and ciliary apparatus
EOM Movement	Lateral rectus palsy	VI CN
	Complete Ophthalmoplegia	Dysfunction of CN III, IV & VI
Visual acuity	↓visual acuity or blindness	Central retinal artery/vein occlusion secondary to ICA arteritis, septic emboli or ischemic optic neuropathy

↓Decreased, ICA internal carotid artery, CN cranial nerve, EOM extraocular muscle

Ocular manifestations of cavernous sinus thrombosis and their underlying pathology

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For those who present at an early stage with nonspecific symptoms (such as headache), a careful eye and neurologic examination, along with thorough cranial nerve testing, is necessary to make the diagnosis.[15] The earliest eye manifestations are caused by venous congestion and include:[4]

- Chemosis (conjunctival edema)
- Periorbital edema
- Proptosis.

Subsequently, the following signs may follow rapidly, as a result of cranial nerve involvement:

- Painful ophthalmoplegia
- Ptosis
- Mydriasis. This may be mid-size only (owing to sympathetic nervous system involvement in the cavernous sinus), causing internal ophthalmoplegia (blunted papillary response to light).

A lateral gaze palsy may develop before full-blown ophthalmoplegia. This is related to the anatomic position of the sixth cranial nerve. Unlike cranial nerves (CNs) III and IV, protected in a fibrous sheath in the lateral wall of the cavernous sinus, CN VI has an intraluminal course, making it susceptible to intracavernous pathology. The ophthalmic branch of the trigeminal nerve (CN V) may also be affected, leading to a decreased corneal reflex.

The sequential involvement of both eyes is indicative of CST. Nevertheless, even before bilateral eye signs have developed, several signs suggestive of septic CST should be sought, including:

- A primary infection site
- Profound sepsis
- Meningismus (nuchal rigidity, photophobia, and headache)
- Early visual impairment
- Pupillary defects
- Fundoscopic abnormalities (papilledema and/or retinal vein dilatation) as well as hypo- or hyperesthesia in the distribution of the ophthalmic and maxillary nerves.

Frequently, these findings are absent in periorbital or orbital cellulitis, for which septic CST is commonly mistaken. Loss of visual acuity is a possible sign, occurring in less than 50% of people with CST.[1] It may be owing to papilledema; corneal ulceration secondary to proptosis and loss of the corneal reflex; occlusion of the internal carotid, ophthalmic, or central retinal artery; orbital congestion; or an embolic phenomenon. If seizure occurs, it should raise suspicion of intracranial suppuration complicating septic CST.

Rarely, patients may have a more indolent form of septic CST and present with:

- Insidious cranial nerve dysfunction
- Minimal signs or symptoms of sepsis
- Unimpressive ocular manifestations related to venous congestion.

A unilateral isolated lateral gaze palsy is the most early sign in subacute septic CST.[15] Bilateral involvement is a late uncommon finding. This presentation could be explained by a slow progressive obliteration of the cavernous sinus, resulting in a higher degree of compensation than that occurring when the occlusion is rapid. It has been postulated to occur when the infection reaches the cavernous sinus in a retrograde direction, such as in otogenic infection, which was more common in the pre-antibiotic era.[50]

The typical pattern of events in aseptic CST is similar but is slower and less dramatic than that of acute septic CST. Signs and symptoms of sepsis or of a primary infection are absent. Sometimes, it is also difficult to distinguish the aseptic from subacute septic varieties of CST. However, in most cases, aseptic CST is associated with an identifiable predisposing condition, such as hypercoagulability state, previous sinus surgery, or neoplasms.

Investigations

Although the diagnosis of septic CST may be made correctly on clinical grounds, this condition frequently co-exists with meningitis or orbital infections; hence, the clinical picture may be confusing.[50] [53] Therefore, any septic patient who develops focal neurologic deficits and orbital signs rapidly requires emergency contrast CT scan and/or MRI of the head to locate the infection.

CT scan and MRI of the head are the primary radiologic modalities used to confirm the diagnosis in all patients and are also used to assess causal and concurrent pathology.[45] [54] Unfortunately, neither modality is entirely sensitive or specific for septic CST. MR venography or CT venography may also be

useful to confirm the diagnosis in patients with suspected CST.[54][55] [56] However, MRV may miss the diagnosis in the dural venous sinuses.[14] A contrast enhanced CT scan is considered superior to MRI for the detection of early clot formation in the cavernous sinuses, whereas MRI is superior for the rest of the dural venous sinuses.[57] MRI may be of greatest value for patients with:

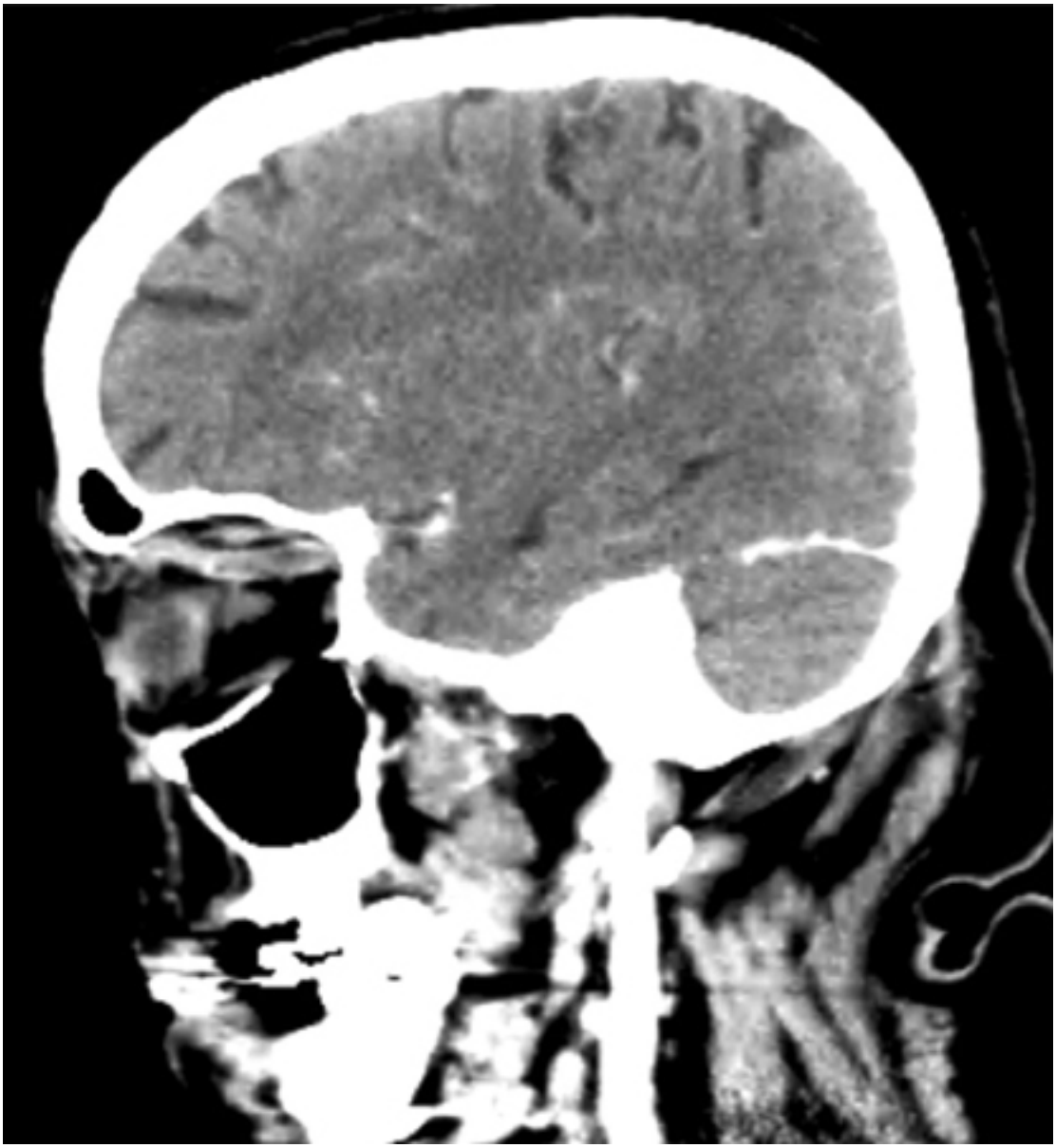
- Nondiagnostic CT scans
- Complications involving the pituitary gland
- Complications involving extension of the infection into the brain.

Angiographic extensions of MRI and CT may also be performed.[58]

Laboratory investigations are performed routinely as initial investigations and reveal a marked leukocytosis on CBC in virtually all cases of septic disease.[4] CBC is also helpful to evaluate for polycythemia as a causative factor and thrombocytopenia, which may suggest thrombotic thrombocytopenic purpura.[59] Leukocytosis may help to distinguish septic from aseptic disease. Bacteriologic confirmation of infection can be obtained from the primary infective source, blood cultures, and concurrent suppuration from relevant, accessible sites.[4] A lumbar puncture may help to exclude meningitis and inform antimicrobial therapy (type and length of therapy) in case a bacterial or fungal agent is isolated.

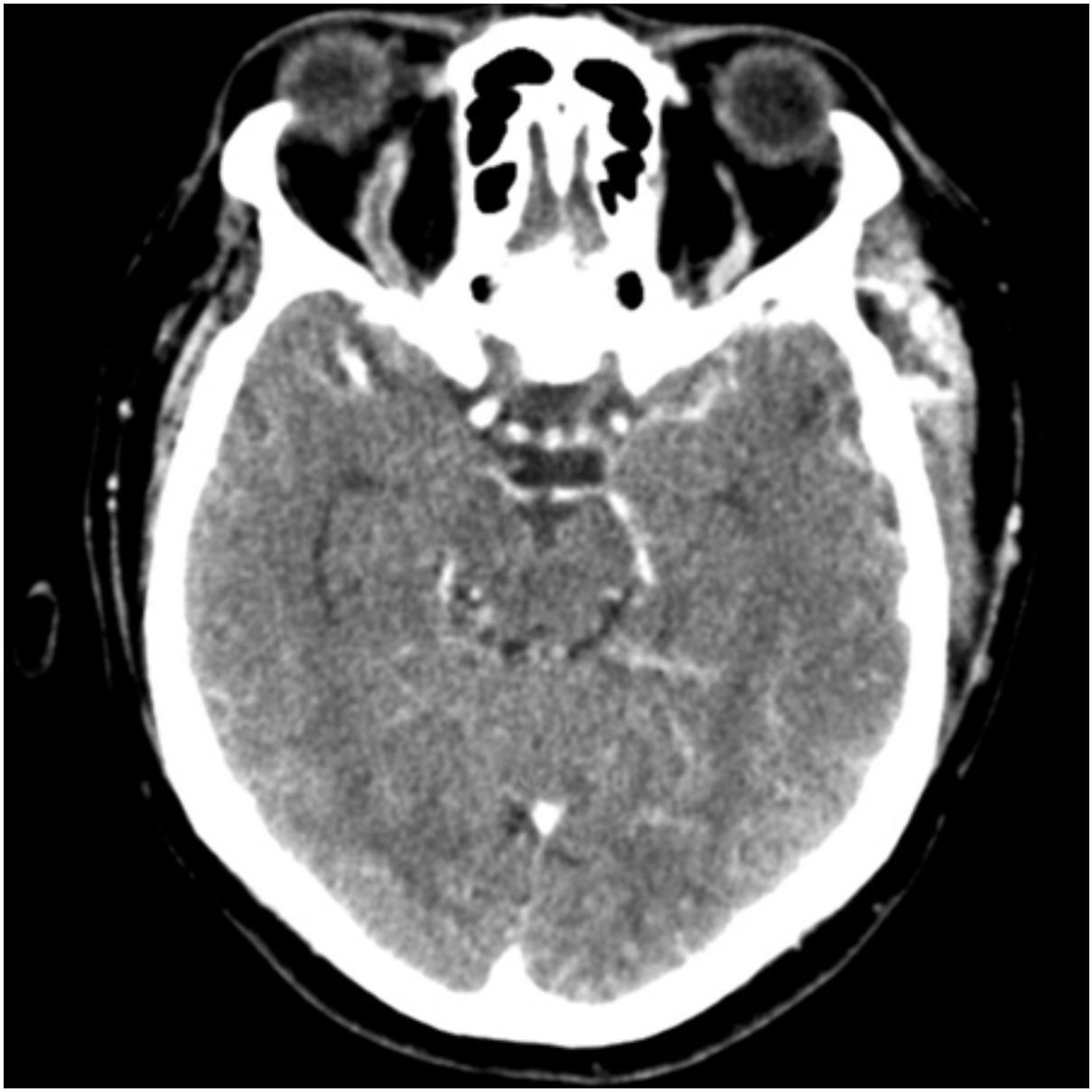
Initial evaluation of hypercoagulable states includes testing for antiphospholipid syndrome (i.e., tests for antiphospholipid and anticardiolipin antibodies).[45] Additional tests for other common causes of hypercoagulable states are indicated, including factor V Leiden, antithrombin III, protein C, and protein S.[45] However, testing for hypercoagulable states may not be indicated if CST is provoked by strong risk factors e.g., recent history of acute sinusitis or facial infections.[60] Thrombophilia testing should not be performed at the time of a VTE event, as it can be inaccurate.[60] Patients should have completed anticoagulant therapy and should not be taking oral anticoagulants at the time of testing, since vitamin K antagonists will decrease protein S and protein C levels, and direct oral anticoagulants can affect clot-based assay results.[60] Hemoglobin electrophoresis is useful in patients who may have sickle cell disease. Consult a hematologist for specialist advice.

Traditional imaging techniques, namely venography and cerebral angiography, have a limited role in the modern diagnosis of septic CST and may be accompanied by serious complications. The use of conventional x-rays (mastoid plain films, sinus plain films, sinus tomograms) has also declined with the use of CT scanning and MRI.



Sagittal CT scan of the head demonstrating an enlarged, tubular right superior ophthalmic vein

Jones RG, Arnold B. Sudden onset proptosis secondary to cavernous sinus thrombosis from underlying mandibular dental infection. BMJ Case Rep. 2009;2009. pii: bcr03.2009.1671. Used with permission



Postcontrast venous phase CT scan of the head (axial view) showing an enlarged 'S'-shaped right superior ophthalmic vein with associated proptosis

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History and exam

Key diagnostic factors

rapid onset of signs and symptoms (acute septic CST) (common)

- The majority of patients have an acute presentation and present in a toxic state.

headache (common)

- Most common early symptom.[51] Reported in 50% to 90% of cases.[4]
- Usually unilateral.
- Usually localized to the regions innervated by the ophthalmic and maxillary branches of cranial nerve V, involving the retro-orbital or frontal areas with occasional radiation to the occipital region.[15]

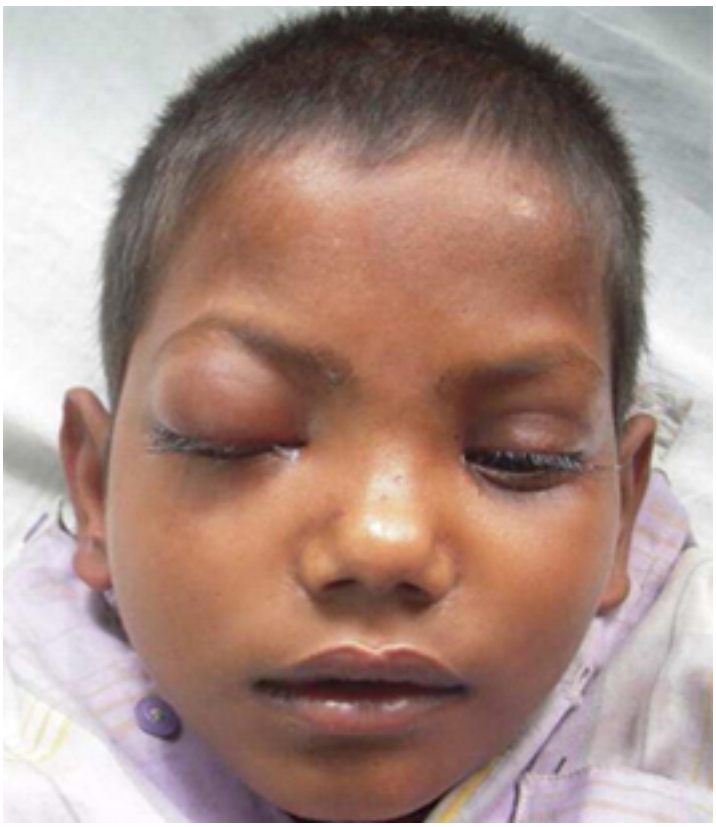
fever (common)

- Occurs in almost all patients with septic CST.[41]
- Is usually high.

periorbital edema (common)

- May be the earliest physical finding.
- Together with chemosis and proptosis, these are the most consistent and visible features of septic CST.[15]
- Caused by venous congestion within orbital veins.
- Spread to the other eye within 24 to 48 hours of the initial unilateral periorbital edema is common and characteristic of septic CST.

chemosis and proptosis (common)

- Together with periorbital edema, these are the most consistent and visible features of septic CST.[13] [15]
- The sequential involvement of both eyes is indicative of acute septic CST.
- Bilateral involvement is a late uncommon finding in the rare subacute septic CST.
- 

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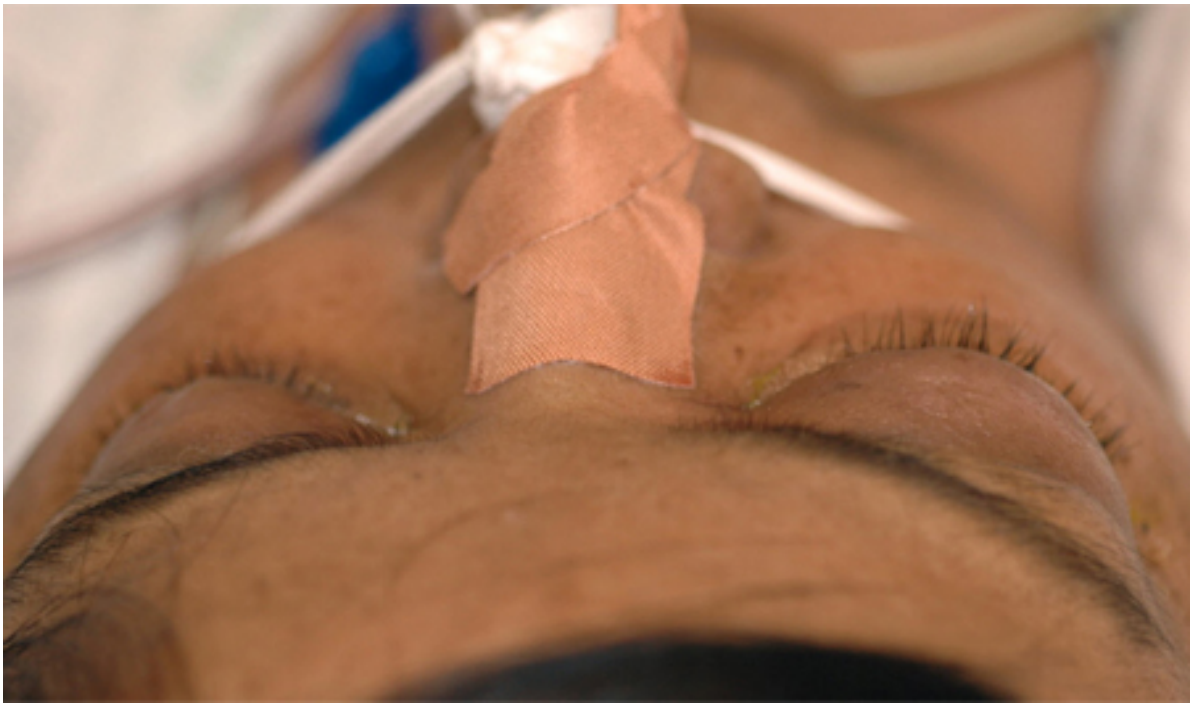

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lateral gaze palsy (common)

- May precede full-blown ophthalmoplegia.
- Unlike cranial nerves (CNs) III and IV, which are located in the lateral wall of the cavernous sinus and protected in a fibrous sheath, CN VI is situated medially and surrounded by blood, making it susceptible to inflammatory damage.
- A unilateral isolated lateral gaze palsy is often an early sign in subacute septic CST.[15]

ophthalmoplegia (common)

- Develops as a result of cranial nerve involvement.
- Often painful.
- The sequential involvement of both eyes is indicative of acute septic CST.
- Bilateral involvement is a late uncommon finding in the rare subacute septic CST.

profound sepsis (acute septic CST) (common)

- Including hypotension, tachycardia, and lethargy.
- Seen in most cases of acute septic CST.
- May help in differentiating septic CST from periorbital or orbital cellulitis.

Other diagnostic factors

ptosis and mydriasis (common)

- Owing to cranial nerve III palsy.
- Mydriasis may be mid-size only (owing to sympathetic nervous system involvement in the cavernous sinus).

papilledema and/or retinal-vein dilatation (common)

- Seen in approximately 65% of cases.[15]
- May help in differentiating septic CST from periorbital or orbital cellulitis.

decreased corneal reflex (common)

- Seen in less than 50% of cases.[1]

hypo- or hyperesthesia in the distribution of the ophthalmic and maxillary nerves (common)

- Signs can be subtle.

mental state changes (e.g., confusion, drowsiness, coma) (common)

- May occur secondary to central nervous system involvement and sepsis may develop rapidly.

clinically detectable primary infection site (common)

- An abnormal otolaryngologic exam, for instance, may include purulent nasal or posterior pharyngeal discharge, inflamed nasal mucosa, and tenderness over the sinuses.

meningismus (nuchal rigidity, photophobia, and headache) (common)

- Seen in as many as 40% of cases.[15]
- May be due to concurrent bacterial meningitis or meningeal irritation.
- Unlikely to be present in periorbital or orbital cellulitis.

positive Kernig or Brudzinski signs (common)

- May be due to concurrent bacterial meningitis or meningeal irritation.
- Unlikely to be present in periorbital or orbital cellulitis.

seizures (uncommon)

- Should raise the suspicion of intracranial suppuration complicating septic CST.

loss of visual acuity (uncommon)

- Reported in less than 50% of cases.[1]
- Can be due to papilledema, corneal ulceration secondary to proptosis and loss of corneal reflex, occlusion of internal carotid, ophthalmic or central retinal artery, orbital congestion or embolic phenomena.
- May help in differentiating septic CST from periorbital or orbital cellulitis.

Risk factors

Strong

recent history of acute sinusitis

- Most prevalent etiology in postantibiotic era.
- The sphenoid and ethmoid sinuses are the most commonly involved.[7] [8] [9] [10] [13] [15]
- Infection from the sphenoid sinuses can spread through communicating veins, through osteomyelitis of the intervening diploic bone or mucosally, if there are bony defects.[39]

- The infection from the ethmoid sinuses spreads indirectly through the ophthalmic veins, after breaching the lamina papyracea.[39]

history of facial infections

- Infection of the middle third of the face was the most common cause of septic cavernous sinus thrombosis (CST) in the pre-antibiotic era.[15] [40]

history of periorbital infection

- Periorbital cellulitis may progress to CST.[41]

genetic prothrombotic condition

- Common risk factor for aseptic CST.
- Includes antithrombin III deficiency, protein C and protein S deficiency, factor V Leiden mutation, prothrombin mutations, and homocysteinemia.[22] [45]

acquired and other prothrombotic states

- Most common risk factor for aseptic CST.
- Includes nephrotic syndrome, polycythemia rubra vera, acute lymphocytic leukemia, antiphospholipid antibodies, pregnancy, and the puerperium.[22] [31]

Weak

history of otitis media, mastoiditis, or petrositis

- The incidence of CST from middle-ear infections has declined owing to the introduction of antibiotics.
- Infection spreads retrograde through the sigmoid sinus.
- Organisms involved include *Pseudomonas aeruginosa* and coagulase-negative *Staphylococcus* .[42]

history of dental or oral infection

- Infection can spread from the maxillary molar teeth to involve the orbit by way of the inferior orbital fissure and can then spread to involve the cavernous sinus.[43] [44]

history of sepsis

- Primary infection may occur at any other site (not just within the head) and includes bacterial meningitis.

immunosuppression

- Mucormycosis (fungal infection of the sinuses, brain, or lungs, usually in people with immunosuppressive conditions) is a cause of septic CST.
- May be either rhinocerebral or otocerebral.[16]

history of head and neck trauma

- Trauma to the orbit or mandible or basilar skull fractures cause aseptic CST.[46] [47]

use of oral contraceptives

- Cases of dural venous thrombosis have been reported to be associated with the intake of oral contraceptive pills.[48]
- This is thought to be especially relevant to the third generation pills, containing gestodene or desogestrel.

pregnant or postpartum

- Women who are pregnant or postpartum may be at increased risk.[4]

history of malignancy

- Specifically, rhabdomyosarcoma, and nasopharyngeal carcinoma.[49]

history of recent head or neck surgery

- May occur postsurgery (e.g., following rhinoplasty, cataract extraction, skull base procedures, and dental extraction).[27] [28] [29]

vascular abnormalities

- Including carotid-cavernous fistula.[33]

ulcerative colitis

- One of several miscellaneous causes.

volume depletion

- One of several miscellaneous causes.

heroin overdose

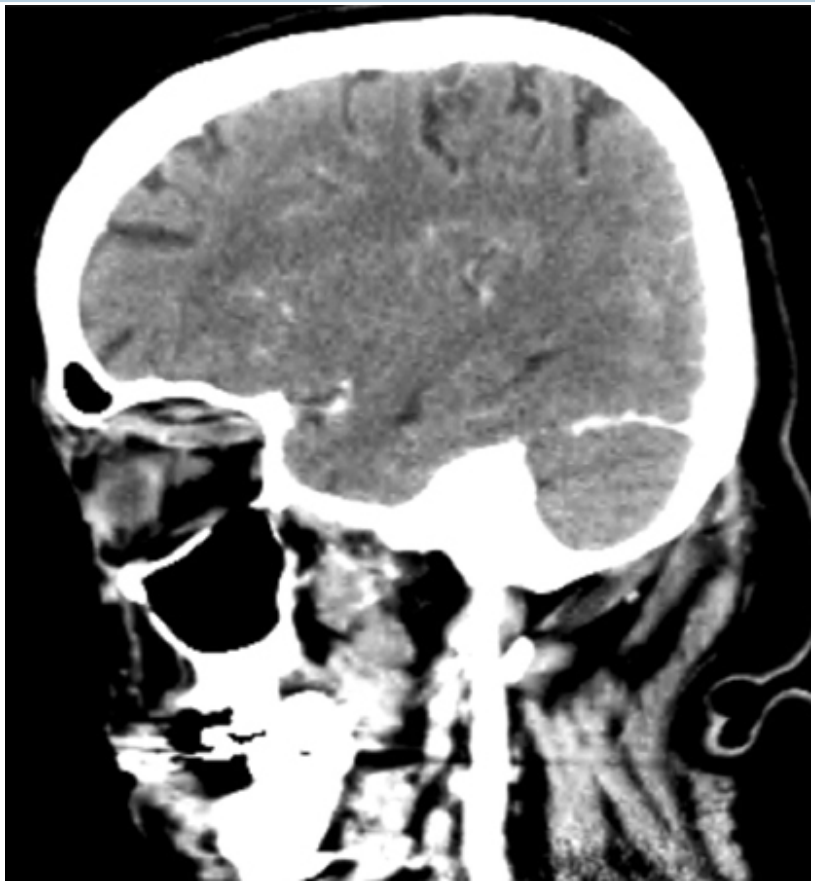
- One of several miscellaneous causes.

Tests

1st test to order

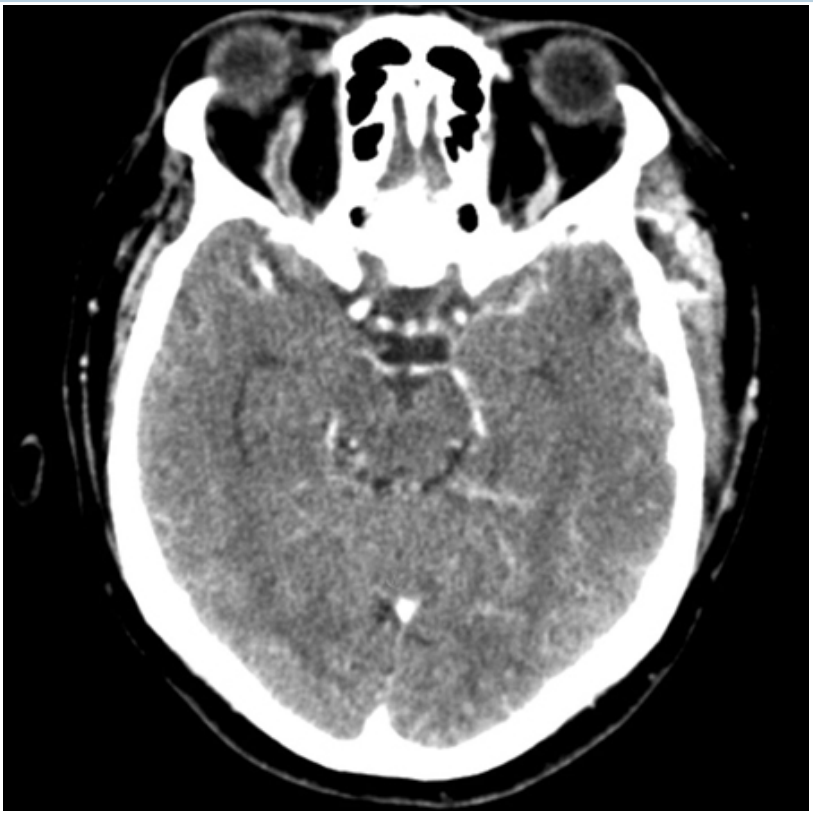
Test	Result
CBC • A marked leukocytosis is present in virtually all cases of septic cavernous sinus thrombosis (CST). This may help to distinguish between septic and aseptic CST. • Anemia is not typical of CST, but if present may suggest disseminated intravascular coagulopathy or sickle cell disease.[61]	**normal or low Hb; marked polymorphonuclear leukocytosis with septic CST**
contrast-enhanced high-resolution CT of head • CT and MRI scan of the head are the primary radiologic modalities used to confirm the diagnosis in all patients and are also used to assess causal and concurrent pathology.[45] [54] Neither is absolutely sensitive or specific for the diagnosis of CST. Contrast enhanced CT scan is considered superior to MRI for the detection of early clot formation in the cavernous sinuses, whereas MRI is superior for the rest of the dural venous sinuses.[57] • CT is performed optimally using a dynamic-scanning technique using a bolus injection and continuous infusion of contrast and with scanning in narrow section intervals (less than 3 mm), performing axial and coronal sections.[62] • Angiographic extensions of CT may also be performed.	**abnormal filling defects together with lateral convexity of the cavernous sinuses**

Test	Result



Sagittal CT scan of the head demonstrating an enlarged, tubular right superior ophthalmic vein

Jones RG, Arnold B. Sudden onset proptosis secondary to cavernous sinus thrombosis from underlying mandibular dental infection. BMJ Case Rep. 2009;2009. pii: bcr03.2009.1671. Used with permission

Test	Result
 *Postcontrast venous phase CT scan of the head (axial view) showing an enlarged 'S'-shaped right superior ophthalmic vein with associated proptosis* *Jones RG, Arnold B. Sudden onset proptosis secondary to cavernous sinus thrombosis from underlying mandibular dental infection. BMJ Case Rep. 2009;2009. pii: bcr03.2009.1671. Used with permission* CT venography may also be useful to confirm the diagnosis in patients with suspected CST.[54][55] [56]	
contrast-enhanced MRI of head • MRI and CT scan of the head are the primary radiologic modalities used to confirm the diagnosis in all patients and are also used to assess causal and concurrent pathology.[45] [54] Neither modality is entirely sensitive or specific for septic CST. • However, contrast enhanced CT scan is considered superior to MRI for the detection of early clot formation in the cavernous sinuses, whereas MRI is superior for the rest of the dural venous sinuses.[57] • May be of greatest value in patients with nondiagnostic CT scans or for evaluating complications involving the pituitary gland or extension of the infection into the brain. • Angiographic extensions of MRI may also be performed. MR venography may also be useful to confirm the diagnosis in patients with suspected CST.[54][55] [56] MRV may miss the diagnosis in the dural venous sinuses.[14]	**expansion of the cavernous sinuses, convex bowing of lateral walls, increased dural enhancement; sphenoid sinus pathology may be present**
blood culture • Bacteriologic confirmation of infection can be obtained in the majority of cases of septic CST from the primary infective source, blood cultures, and concurrent suppuration from relevant, accessible sites.	**septic CST: may be positive**

Test	Result
microscopy and culture of suppurative fluid or tissue from primary infective source • Bacteriologic confirmation can be obtained in the majority of cases of septic CST from the primary infective source, blood cultures, and concurrent suppuration from relevant, accessible sites.	**septic CST: positive culture of offending organism**
antiphospholid and anticardiolipin antibodies • Performed as part of testing for antiphospholipid syndrome. Testing for hypercoagulable states may not be indicated if CST is provoked by strong risk factors e.g., recent history of acute sinusitis or facial infections.[60] Consult a hematologist for specialist advice.	**elevated levels indicate a hypercoagulable state**
protein S and protein C • Performed as part of testing for a hypercoagulable state. Testing for hypercoagulable states may not be indicated if CST is provoked by strong risk factors e.g., recent history of acute sinusitis or facial infections.[60] Consult a hematologist for specialist advice.	**low level or deficiency indicates hypercoagulable state**
antithrombin III • Performed as part of testing for a hypercoagulable state. Testing for hypercoagulable states may not be indicated if CST is provoked by strong risk factors e.g., recent history of acute sinusitis or facial infections.[60] Consult a hematologist for specialist advice.	**low level or deficiency indicates hypercoagulable state**
factor V Leiden • Performed as part of testing for a hypercoagulable state. Testing for hypercoagulable states may not be indicated if CST is provoked by strong risk factors e.g., recent history of acute sinusitis or facial infections.[60] Consult a hematologist for specialist advice.	**presence indicates hypercoagulable state**
hemoglobin electrophoresis • Only performed in patients with clinical suspicion of sickle cell disease.	**hemoglobin S detected in sickle cell disease**

Other tests to consider

Test	Result
lumbar puncture with cerebrospinal fluid analysis • May help to exclude meningitis and inform antimicrobial therapy (type and length of therapy) in case a bacterial or fungal agent is isolated.	**elevated CSF pressure; inflammatory cells; offending organisms may be detected**

Differentials

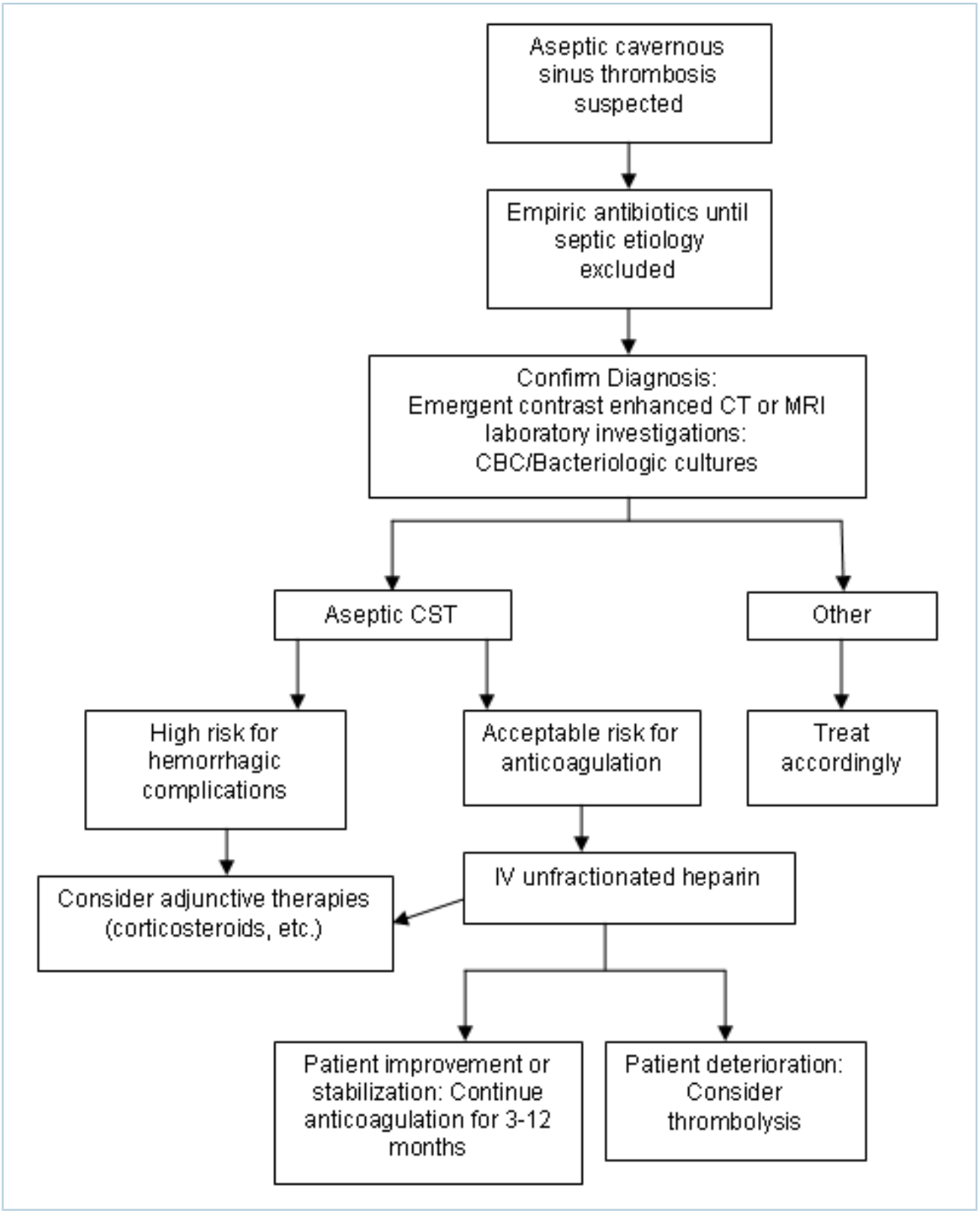
Condition	Differentiating signs / symptoms	Differentiating tests
Periorbital or orbital cellulitis	• Visual symptoms are more prominent in orbital cellulitis because of the involvement of the optic nerve. • May manifest in only one eye, whereas CST progresses more commonly to both eyes.[63] • Less likely to have profound sepsis, meningeal signs, and early fixation of the globe compared with CST.[63] [64]	• CT scan and MRI of the head can differentiate between early CST and periorbital or orbital cellulitis by the presence of enlargement and expansion of the cavernous sinus in CST.[64] • If a lumbar puncture is performed, 75% of people with septic CST will have inflammatory cells on cerebrospinal fluid analysis, unlike people with periorbital or orbital cellulitis.
Superior orbital fissure syndrome	• Presents as ocular pain, proptosis, external ophthalmoplegia (owing to the paralysis of cranial nerves III, IV, VI) and neuralgic pain/anesthesia of the involved areas supplied by the first and second branch of the trigeminal nerve.[65] • All differentiating features are subtle and relative.	• CT scan or MRI of the head will show involvement of the cavernous sinuses in CST.
Orbital apex syndrome	• Presents with internal and external ophthalmoplegia, visual loss, and trigeminal nerve (cranial nerve V1) anesthesia. Visual impairment present because of optic nerve involvement. This is less likely to be a feature in CST. • Trigeminal nerve anesthesia is also a differentiating sign.	• CT scan or MRI of the head will show involvement of the cavernous sinuses in CST.
Sino-orbital aspergillosis	• Presentation similar to superior orbital fissure syndrome. • All differentiating features are subtle and relative.	• CT scan or MRI of the head will show involvement of the cavernous sinuses in CST.
Subperiosteal mucoceles	• Presentation similar to superior orbital fissure syndrome. • All differentiating features are subtle and relative.	• CT scan or MRI of the head will show involvement of the cavernous sinuses in CST.

Condition	Differentiating signs / symptoms	Differentiating tests
Tolosa-Hunt syndrome	• Presentation the same as superior orbital fissure syndrome. • All differentiating features are subtle and relative. • Characteristically, responds well to corticosteroids.[66]	• Clinical diagnosis may be differentiating. • MRI of the head, with and without contrast, is useful in demonstrating inflammatory changes in the superior orbital fissure/orbital apex or the cavernous sinus.
Meningioma	• Location can be either spheno-orbital, superior orbital fissure, or cavernous sinus. • Presenting signs depend on the site of involvement but, generally, this diagnosis results in focal neurologic symptoms. • There is generally an absence of sepsis, fever, and bilateral eye involvement.	• MRI of the head demonstrating the meningioma as hyperintense on T1, mixed intensity on T2, and enhancement with gadolinium with a dural tail sign (extension of a mass toward the dura giving the appearance of a tail).
Carotid-cavernous fistula	• Usually a history of trauma, especially basilar skull fractures.[67] [68] • Can also be caused by rupture of an intracavernous carotid aneurysm or an atherosclerotic internal carotid artery and there may be a history of these conditions.[69] • Can either be direct with shunts between the cavernous sinus and the internal carotid or as dural shunts between the cavernous sinus and the meningeal branches of the internal or external carotid artery.[69] • The direct shunt usually causes pulsatile exophthalmos, in addition to the other symptoms of ophthalmoplegia, a reduced visual acuity and venous congestion.[70]	• MRI/magnetic resonance angiography (MRA) or carotid angiography: these tests will demonstrate blockage of the cavernous sinus in CST compared with abnormal connections between the carotid and cavernous sinus in carotid-cavernous fistula.
Rhinocerebral mucormycosis	• Usually occurs in immunocompromised patients, especially people with diabetes mellitus, renal failure, or neutropenia.[71]	• CT scan or MRI of the head will show significant invasion of bone and blood vessels. • There is characteristic hypodensity on T2-weighted MRI.[72]

Condition	Differentiating signs / symptoms	Differentiating tests
	• Characterized by the presence of black necrotic eschar in the nasal cavity, invasion of bone and blood vessels, and earlier exophthalmos.[72]	• CT scan or MRI of the head will show involvement of the cavernous sinuses in CST.

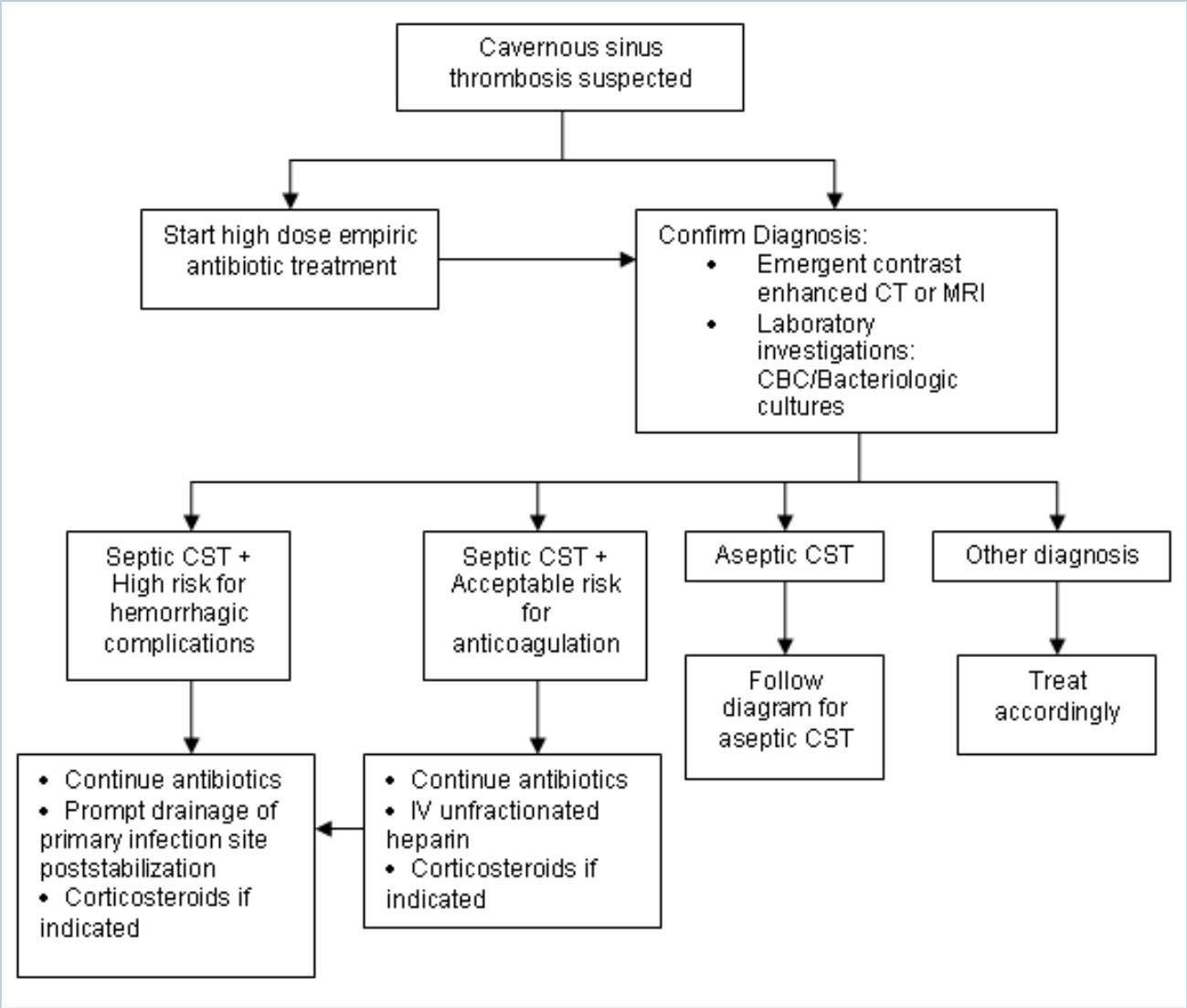
Approach

The overall mortality and morbidity associated with cavernous sinus thrombosis (CST) continues to be high.[15] Consequently, institution of intensive treatment at the earliest suspicion of disease should be emphasized. Antibiotics are the mainstay of CST therapy. Anticoagulation, corticosteroids, and surgery are adjunctive treatment in appropriately selected patients. Because it is often difficult to distinguish between septic and nonseptic causes of CST, the initial management is the same. Only when a septic etiology is ruled out definitively can antibiotics be withdrawn. In practice, therefore, the treatments are the same for both aseptic and septic disease.



Treatment of aseptic cavernous sinus thrombosis (CST)

From the collection of Dr Jayant Pinto, University of Chicago



Treatment of septic cavernous sinus thrombosis (CST)

From the collection of Dr Jayant Pinto, University of Chicago

Initial therapy in all patients

Based on case reports and expert opinion, antibiotics are recommended as the mainstay of therapy. They have the greatest impact on the prognosis of septic CST.[2] High-dose intravenous antibiotics should be instituted at the earliest suspicion of this diagnosis.[2] Appropriate selection of empiric antibiotic regimens should be directed at the probable organisms implicated as the primary source of infection. It is necessary to take into account possible complications, such as brain or orbital abscesses, meningitis, or subdural empyema.[1] [50]

Staphylococcus aureus is the most common pathogen, identified in approximately 70% of cases and is the pathogen implicated in nearly all cases of facial infections.[1] Bacteria associated with sinusitis include *Fusobacterium necrophorum* and Streptococci (including *S pneumoniae*, *S milleri*, and *S viridans* group).[13] Anaerobes are found occasionally, especially with sinus, dental, or tonsillar infections. Rarely, fungal infection from *Aspergillus fumigatus* or mucormycosis have been implicated in CST.[73] [74]

For empiric antibiotic therapy, the Infectious Diseases Society of America (IDSA) guideline recommends vancomycin for 4-6 weeks with or without rifampin.[75] Alternative options may include linezolid or

trimethoprim/sulfamethoxazole.[75] However, these guidelines were published in 2011 and no evidence-based guidelines on empiric antibiotics for this indication have been published since. Some experts do not recommend vancomycin unless the patient is known to be colonized with MRSA. Other options, based on expert opinion, may include amoxicillin/clavulanate plus gentamicin, a third-generation cephalosporin, a fluoroquinolone, and the addition of metronidazole if brain abscess or dental or sinus infection is suspected.[6] [76][77] [78] Consult your local guidelines or infectious disease specialist for more information as this is a very specialized area with little evidence available to guide treatment decisions.

Antifungal therapy has been advocated only in cases of biopsy-confirmed invasive fungal infection. However, in at-risk patients, antifungal treatment should be considered as fungi may cause devastating neurological complications beyond cerebral venous thrombosis.[79]

As soon as the laboratory has reported sensitivities, empiric antibiotics can be switched to specific antibiotic therapy.

High doses of intravenous antibiotics are required because thrombus may limit penetration of antibiotics. Bacteria, sequestered within the thrombus, may not be killed until the dural sinuses have started to recanalize. Antibiotics also need to be administered over an extended period, for at least 3-4 weeks.[41] This aims to insure complete sterilization and prevent relapses.

Concurrent supportive therapy is necessary alongside antibiotic treatment, and includes resuscitation, oxygen support, and local eye care.[4]

Adjunctive therapy: anticoagulation

Considerable controversy exists concerning the efficacy of anticoagulation in the treatment of CST.[41] Prospective trials to establish any benefit from anticoagulation have never been (and are unlikely to be) performed owing to the rarity of the condition.[41] Anticoagulation carries the risk of hemorrhage, especially in patients with concomitant complications (e.g., cortical venous infarction, necrosis of intracavernous portions of the carotid artery, and cerebral or intraorbital hemorrhages).[50] However, there is some evidence that the use of anticoagulation prevents propagation and contributes to recanalization of the thrombus. These are potentially beneficial effects, partly because the thrombus itself can harbor bacteria and sustain their growth.[2] Two retrospective reviews examining the use of anticoagulation for septic CST produced varying results.[15] [22]

Currently, evidence is accumulating for the efficacy of anticoagulation in other forms of dural venous thrombosis. There have been two controlled trials comparing the use of placebo to anticoagulants in patients with cerebral sinus venous thrombosis.[80] [81] European Federation of Neurological Societies (EFNS) guidelines recommend either subcutaneous low molecular weight heparin or intravenous heparin for aseptic dural venous thrombosis.[82] Similarly, guidelines published by the European Paediatric Neurology Society (EPNS) in 2012 recommend the use of anticoagulants for dural venous thrombosis to lessen the risk of death and other sequelae.[83] However, it should be noted that septic CST and aseptic dural venous thrombosis differ in many respects and that anticoagulation may be more hazardous in patients with septic CST.[50] The differences include the presence of infective etiology, the site of the thrombosis, the acuteness of the process, and the presence of associated hemorrhagic complications.[50]

Based on limited observation, anticoagulation may be beneficial after exclusion of hemorrhagic complications by CT scan.[2] [15] [22] Anticoagulation is thought by some to be dangerous in patients with bilateral CST and/or concurrent intracranial hemorrhage.

The types and protocols for anticoagulation have varied considerably in research protocols. Intravenous and intramuscular unfractionated heparin, subcutaneous low molecular-weight heparin, and oral anticoagulation have all been used. However, the use of a rapidly reversible agent, such as intravenous unfractionated heparin has been advocated in the early stages of disease, followed by conversion to longer-acting agents, such as warfarin, when the patient's condition has stabilized.[50] One systematic review and meta-analysis suggested that in patients with cerebral venous thrombosis, direct oral anticoagulants (DOACs), and warfarin may have comparable efficacy and safety.[84] The evidence for the use of DOACs for CVT is limited.[85]

Newer anticoagulants, including direct thrombin inhibitors and factor Xa inhibitors, offer many advantages over heparin, including a more predictable anticoagulant effect and an absence of induction of immune-mediated heparin-induced thrombocytopenia (HIT).[86] However, there is a lack of reported cases of CST or other forms of dural sinus thrombosis that have been treated with these agents. The use of direct thrombin inhibitors, such as argatroban, can be considered as an alternate form of anticoagulation to heparin in patients with HIT or those at risk of HIT.

The duration of anticoagulation has not been determined and varies in reports from a few weeks to several months.[4] [6] Some authors have suggested that anticoagulation should be continued until clinical or radiologic evidence of complete resolution is present, or until there is significant improvement of the infection and thrombus.

Patients commenced on anticoagulants are usually still in an unstable clinical condition and are therefore not candidates for surgical management. However, if the patient's condition stabilizes and surgical management is indicated, rapidly reversible anticoagulants can be discontinued to allow surgery.

If a patient is considered suitable for anticoagulation but deteriorates despite this therapy, they may be considered for endovascular therapy.[87] [88] [89] Although endovascular treatment is increasingly being used to treat patients with cerebral venous thrombosis, this treatment is not routinely recommended in all patients.[90] This therapy is usually reserved for progressive, aseptic CST and carries with it the risks of intracranial hemorrhage, stroke, and the inability to recanalize. It does not preclude corticosteroids.

Adjunctive therapy: corticosteroids

The role of corticosteroids is controversial in many cases of CST. They are potentially harmful because of their immunosuppressive effects. However, corticosteroids are absolutely indicated in cases of pituitary insufficiency. Corticosteroid use may have a critical role in patients with Addisonian crisis secondary to ischemia or necrosis of the pituitary that complicates CST.[91] [92]

Although there would seem to be only empiric support for their anti-inflammatory properties, with a real fear of progression to generalized sepsis, corticosteroids may also be beneficial for:[4]

- Reducing intraorbital congestion in patients with orbital edema
- Reducing cranial nerve inflammation in patients with cranial nerve dysfunction.

There are only a few anecdotal reports concerning the use of corticosteroids in CST in general and their efficacy has not been confirmed by these reports. In the studies in which the use of corticosteroids has been reported, other treatments have been used concurrently.[15] [39] [93] [94] In one case, reported in 1962, cranial nerve dysfunction and orbital edema failed to improve after 37 days of antibiotic and anticoagulant therapy but regressed dramatically 2 days after the addition of corticosteroid therapy, with eventual complete resolution in eye signs and symptoms.[95]

Surgical drainage post-stabilization

Finally, as soon as the patient's condition permits, prompt drainage of the primary site of infection (such as the paranasal sinusitis, dental abscess) or other concurrent closed-space infection is advisable.[7] [15] [96]

Surgical drainage of the cavernous sinus is almost never performed.[1]

In sinogenic CST, surgical drainage of the sinuses for all cases has been advocated.[11] [12] [13] Different operations have been performed to decompress the sinuses, including transseptal sphenoidectomy, endoscopic sphenoidectomy and ethmoidectomy and external fronto-ethmoidal-sphenoidectomy. In cases of otogenic CST, mastoidectomy has been performed, with decompression of sigmoid sinus thrombophlebitis.[42]

Treatment algorithm overview

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer

Initial		(summary)
suspected CST		
	1st	**empiric antibiotic therapy + supportive therapy**

Acute		(summary)
confirmed septic CST: without hemorrhagic complications		
	1st	targeted antibiotic therapy + supportive therapy
	plus	consider heparin or argatroban
	adjunct	intravenous corticosteroids
	plus	surgical drainage post-stabilization
	plus	switch to warfarin post-stabilization
confirmed septic CST: with hemorrhagic complications		
	1st	targeted antibiotic therapy + supportive therapy
	adjunct	intravenous corticosteroids
	plus	surgical drainage post-stabilization
confirmed aseptic CST: without hemorrhagic complications		
	1st	supportive therapy
	plus	heparin or argatroban
	adjunct	endovascular therapy
	adjunct	intravenous corticosteroids
	plus	switch to warfarin post-stabilization
confirmed aseptic CST: with hemorrhagic complications		
	1st	supportive therapy
	adjunct	intravenous corticosteroids

Treatment algorithm

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer

Initial

suspected CST

1st **empiric antibiotic therapy + supportive therapy**

» High-dose intravenous antibiotics should be instituted at the earliest suspicion of this diagnosis.[2]

» Appropriate selection of empiric antibiotic regimens should be directed at the probable organisms implicated at the primary source of infection.

» For empiric antibiotic therapy, the Infectious Diseases Society of America (IDSA) guideline recommends vancomycin for 4-6 weeks with or without rifampin.[75] Alternative options may include linezolid or trimethoprim/sulfamethoxazole.[75] However, these guidelines were published in 2011 and no evidence-based guidelines on empiric antibiotics for this indication have been published since. Some experts do not recommend vancomycin unless the patient is known to be colonized with MRSA. Other options, based on expert opinion, may include amoxicillin/clavulanate plus gentamicin, a third-generation cephalosporin, a fluoroquinolone, and the addition of metronidazole if brain abscess or dental or sinus infection is suspected.[6] [76][77] [78] Consult your local guidelines or infectious disease specialist for more information as this is a very specialized area with little evidence available to guide treatment decisions.

» Antifungal therapy is required rarely and has been advocated only in cases of biopsy-confirmed invasive fungal infection.

» As soon as the laboratory has reported sensitivities, empiric antibiotics can be switched to specific antibiotic therapy.

» High doses of intravenous antibiotics are required. They also need to be administered over an extended period; for at least 3-4 weeks beyond the time of clinical resolution.[41]

» Concurrent supportive therapy is necessary alongside antibiotic treatment, and includes

Initial

resuscitation, oxygen support, and local eye care.

Acute

confirmed septic CST: without hemorrhagic complications

1st **targeted antibiotic therapy + supportive therapy**

» As soon as the laboratory has reported sensitivities, empiric antibiotics can be switched to specific antibiotic therapy.

» High doses of intravenous antibiotics are required. They also need to be administered over an extended period; for at least 3-4 weeks beyond the time of clinical resolution.[41]

» Antifungal therapy is required rarely and has been advocated only in cases of biopsy-confirmed invasive fungal infection. However, in at-risk patients, antifungal treatment should be considered as fungi may cause devastating neurologic complications beyond cerebral venous thrombosis.[79]

» Concurrent supportive therapy is necessary alongside antibiotic treatment, and includes resuscitation, oxygen support, and local eye care.[4]

plus **consider heparin or argatroban**

Treatment recommended for ALL patients in selected patient group

Primary options

» heparin: 80 units/kg intravenous bolus initially, followed by a 18 units/kg/hour intravenous infusion titrated to an activated partial thromboplastin time (aPTT) between 1.5 and 2.5

OR

» argatroban: consult specialist for guidance on dose

» Considerable controversy exists concerning the efficacy of anticoagulation. Evidence concerning effects on mortality and morbidity has been inconsistent.[41]

» There is a risk of hemorrhage but there is some evidence that it prevents propagation and contributes to recanalization of the thrombus.

» Anticoagulation is contraindicated in intracerebral hemorrhage, subarachnoid hemorrhage, and bleeding diathesis. Some also consider it to be dangerous in patients with

Acute

bilateral CST. Based on limited observation, it may be beneficial after exclusion of hemorrhagic complications by CT scan.[2] [15] [22]

» Intravenous unfractionated heparin has been advocated in the early stages. This can be switched to longer-acting agents, such as warfarin, when the patient's condition has stabilized.[50] One systematic review and meta-analysis suggested that in patients with cerebral venous thrombosis, direct oral anticoagulants (DOACs), and warfarin may have comparable efficacy and safety.[84] The evidence for the use of DOACs for CVT is limited.[85]

» Direct thrombin inhibitors, such as argatroban, can be considered as an alternate form of anticoagulation to heparin in patients with, or at risk of, heparin-induced thrombocytopenia.[97]

» The required duration of anticoagulation has not been determined.[4] [6]

adjunct **intravenous corticosteroids**

Treatment recommended for SOME patients in selected patient group

Primary options

» hydrocortisone: 100 mg intravenously every 6 hours

OR

» dexamethasone sodium phosphate: 10 mg intravenously every 6 hours

» The role of corticosteroids is controversial in many cases of CST. They are potentially harmful because of their immunosuppressive effects.

» However, corticosteroids are absolutely indicated in cases of pituitary insufficiency. Corticosteroid use may have a critical role in patients with Addisonian crisis secondary to ischemia or necrosis of the pituitary that complicates CST.[91] [92]

» Although there would seem to be only empiric support for its anti-inflammatory properties, with real fear of generalized sepsis, the use of corticosteroids may be considered and prove helpful in reducing cranial nerve inflammation and secondary cranial nerve dysfunction and also in decreasing orbital edema.[4]

» There are only a few anecdotal reports documented concerning the use of

Acute

corticosteroids but their efficacy cannot be confirmed by these reports because other treatments have been used at the same time.[15] [39] [93] [94]

plus **surgical drainage post-stabilization**

Treatment recommended for ALL patients in selected patient group

» As soon as the patient's condition permits, prompt drainage of the primary site of infection (such as paranasal sinusitis or dental abscess) or other concurrent closed-space infection is advisable.[7] [15] [96] Surgical drainage of the cavernous sinus is almost never performed.[1]

» In sinogenic CST, surgical drainage of the sinuses for all cases has been advocated.[11]

» Different operations have been performed to decompress the sinuses, including transseptal sphenoidectomy, endoscopic sphenoidectomy and ethmoidectomy, as well as external fronto-ethmoidal-sphenoidectomy.

» In cases of otogenic CST, mastoidectomy has been performed with decompression of sigmoid sinus thrombophlebitis.[42]

plus **switch to warfarin post-stabilization**

Treatment recommended for ALL patients in selected patient group

Primary options

» warfarin: commenced following stabilization of the condition with heparin or argatroban; heparin or argatroban is discontinued as warfarin is commenced: see local specialist protocol for dosing guidance

» When the patient has been stabilized, heparin or argatroban can be substituted with longer-acting anticoagulation such as warfarin.[50] One systematic review and meta-analysis suggested that in patients with cerebral venous thrombosis, direct oral anticoagulants (DOACs), and warfarin may have comparable efficacy and safety.[84] The evidence for the use of DOACs for CVT is limited.[85]

confirmed septic CST: with hemorrhagic complications

1st **targeted antibiotic therapy + supportive therapy**

MANAGEMENT

Acute

» As soon as the laboratory has reported sensitivities, empiric antibiotics can be switched to specific antibiotic therapy.

» High doses of intravenous antibiotics are required. They also need to be administered over an extended period; for at least 3-4 weeks beyond the time of clinical resolution.[41]

» Antifungal therapy is required rarely and has been advocated only in cases of biopsy-confirmed invasive fungal infection.

» Concurrent supportive therapy is necessary alongside antibiotic treatment, and includes resuscitation, oxygen support, and local eye care.[4]

adjunct **intravenous corticosteroids**

Treatment recommended for SOME patients in selected patient group

Primary options

» hydrocortisone: 100 mg intravenously every 6 hours

OR

» dexamethasone sodium phosphate: 10 mg intravenously every 6 hours

» The role of corticosteroids is controversial in many cases of CST. They are potentially harmful because of their immunosuppressive effects.

» However, corticosteroids are absolutely indicated in cases of pituitary insufficiency. Corticosteroid use may have a critical role in patients with Addisonian crisis secondary to ischemia or necrosis of the pituitary that complicates CST.[91] [92]

» Although there would seem to be only empiric support for its anti-inflammatory properties, with real fear of generalized sepsis, the use of corticosteroids may be considered and prove helpful in reducing cranial nerve inflammation and secondary cranial nerve dysfunction and also in decreasing orbital edema.[4]

» There are only a few anecdotal reports documented concerning the use of corticosteroids but their efficacy cannot be confirmed by these reports because other treatments have been used at the same time.[15] [39] [93] [94]

Acute

plus **surgical drainage post-stabilization**

Treatment recommended for ALL patients in selected patient group

» As soon as the patient's condition permits, prompt drainage of the primary site of infection (such as para-nasal sinusitis or dental abscess) or other concurrent closed-space infection is advisable.[7] [15] [96] Surgical drainage of the cavernous sinus is almost never performed.[1]

» In sinogenic CST, surgical drainage of the sinuses for all cases has been advocated.[11]

» Different operations have been performed to decompress the sinuses, including transseptal sphenoidectomy, endoscopic sphenoidectomy and ethmoidectomy, as well as external fronto-ethmoidal-sphenoidectomy.

» In cases of otogenic CST, mastoidectomy has been performed with decompression of sigmoid sinus thrombophlebitis.[42]

confirmed aseptic CST: without hemorrhagic complications

1st **supportive therapy**

» Concurrent supportive therapy is necessary and includes resuscitation, oxygen support, and local eye care.[4]

plus **heparin or argatroban**

Treatment recommended for ALL patients in selected patient group

Primary options

» heparin: 80 units/kg intravenous bolus initially, followed by a 18 units/kg/hour intravenous infusion titrated to an activated partial thromboplastin time (aPTT) between 1.5 and 2.5

OR

» argatroban: consult specialist for guidance on dose

» Considerable controversy exists concerning the efficacy of anticoagulation. Evidence concerning effects on mortality and morbidity has been inconsistent.[41]

» There is a risk of hemorrhage but there is some evidence that it prevents propagation and contributes to recanalization of the thrombus.

Acute

» Anticoagulation is contraindicated in intracerebral hemorrhage, subarachnoid hemorrhage, and bleeding diathesis. Some also consider it to be dangerous in patients with bilateral CST. Based on limited observation, it may be beneficial after exclusion of hemorrhagic complications by CT scan.[2] [15] [22]

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» Direct thrombin inhibitors, such as argatroban, can be considered as an alternate form of anticoagulation to heparin in patients with, or at risk of, heparin-induced thrombocytopenia.[97]

» The required duration of anticoagulation has not been determined.

adjunct **endovascular therapy**

Treatment recommended for SOME patients in selected patient group

» If a patient is considered suitable for anticoagulation but deteriorates despite this therapy, they may be considered for endovascular treatment.[87] [88] [89] Although endovascular treatment is increasingly being used to treat patients with cerebral venous thrombosis, this treatment is not routinely recommended in all patients.[90] This therapy is usually reserved for progressive, aseptic CST and carries with it the risks of intracranial hemorrhage, stroke, and the inability to recanalize. It does not preclude corticosteroids.

adjunct **intravenous corticosteroids**

Treatment recommended for SOME patients in selected patient group

Primary options

» hydrocortisone: 100 mg intravenously every 6 hours

OR

» dexamethasone sodium phosphate: 10 mg intravenously every 6 hours

Acute

» The role of corticosteroids is controversial in many cases of CST. They are potentially harmful because of their immunosuppressive effects.

» However, corticosteroids are absolutely indicated in cases of pituitary insufficiency. Corticosteroid use may have a critical role in patients with Addisonian crisis secondary to ischemia or necrosis of the pituitary that complicates CST.[91] [92]

» Although there would seem to be only empiric support for its anti-inflammatory properties, with real fear of generalized sepsis, the use of corticosteroids may be considered and prove helpful in reducing cranial nerve inflammation and secondary cranial nerve dysfunction and also in decreasing orbital edema.[4]

» There are only a few anecdotal reports documented concerning the use of corticosteroids but their efficacy cannot be proved by these reports because other treatments have been used at the same time.[15] [39] [93] [94]

plus **switch to warfarin post-stabilization**

Treatment recommended for ALL patients in selected patient group

Primary options

» warfarin: commenced following stabilization of the condition with heparin or argatroban; heparin or argatroban is discontinued as warfarin is commenced: see local specialist protocol for dosing guidance

» When the patient has been stabilized, heparin or argatroban can be substituted with longer-acting anticoagulation such as warfarin.[50] One systematic review and meta-analysis suggested that in patients with cerebral venous thrombosis, direct oral anticoagulants (DOACs), and warfarin may have comparable efficacy and safety.[84] The evidence for the use of DOACs for CVT is limited.[85]

confirmed aseptic CST: with hemorrhagic complications

1st **supportive therapy**

» Concurrent supportive therapy is necessary and includes resuscitation, oxygen support, and local eye care.[41]

adjunct **intravenous corticosteroids**

MANAGEMENT

Acute

Treatment recommended for SOME patients in selected patient group

Primary options

» hydrocortisone: 100 mg intravenously every 6 hours

OR

» dexamethasone sodium phosphate: 10 mg intravenously every 6 hours

» The role of corticosteroids is controversial in many cases of CST. They are potentially harmful because of their immunosuppressive effects.

» However, corticosteroids are absolutely indicated in cases of pituitary insufficiency. Corticosteroid use may have a critical role in patients with Addisonian crisis secondary to ischemia or necrosis of the pituitary that complicates CST.[91] [92]

» Although there would seem to be only empiric support for its anti-inflammatory properties, with real fear of generalized sepsis, the use of corticosteroids may be considered and prove helpful in reducing cranial nerve inflammation and secondary cranial nerve dysfunction and also in decreasing orbital edema.[4]

» There are only a few anecdotal reports documented concerning the use of corticosteroids but their efficacy cannot be confirmed by these reports because other treatments have been used at the same time.[15] [39] [93] [94]

Primary prevention

Discouraging patients from manipulating facial furuncles and using systemic antibiotic prophylaxis before surgical drainage of infections at sites that drain to the cavernous sinus may prevent septic cavernous sinus thrombosis.[50]

Patient discussions

Patients should be monitored by family for signs of neurologic deterioration, infection (e.g., fever), and change in mental status. Patients taking anticoagulation should receive training on prevention of falls, monitoring of relevant coagulation parameters, and interactions with other blood-thinning agents. Withdrawal of anticoagulation can be considered at a deferred time frame, typically several weeks to months. This will depend on the resolution of both the clinical symptoms and imaging. Close,

multidisciplinary follow-up is required with neurology, neurosurgery, infectious disease, endocrinology, and hematology specialists.

FOLLOW UP

Monitoring

Monitoring

Patients should be followed up regularly for several months after discontinuation of antibiotic treatment. Relapses of septic cavernous sinus thrombosis (CST), indicated by recurrence of meningismus or ocular signs, have been reported up to 6 weeks after an apparent recovery and brain abscesses have been reported up to 8 months later.[57] [96]

FOLLOW UP

Complications

Complications	Timeframe	Likelihood
death	**short term**	**high**
Mortality has decreased from 80% to 100% in the pre-antibiotic era to 20% to 30% at the present time.[1] [4] The decrease in mortality rate is owing to early diagnosis of infection and rapid treatment with intravenous antibiotics, the most important factor to alter the prognosis of the disease.[2] In addition, surgical management of the primary source of infection (e.g., endoscopic sinus surgery), lowers mortality.[12] [13] [14]		
meningitis	**short term**	**medium**
Presents with fever, chills, nuchal rigidity, and mental status changes. Diagnosis can be made with lumbar puncture and cerebrospinal fluid analysis.		
septic embolization	**short term**	**medium**
Metastatic infection most commonly involves the lungs, the skin, kidney or bone (14%), the orbit (18%), or the brain (10%).[37] [46]		
intracranial hemorrhage secondary to anticoagulation or thrombolysis	**short term**	**medium**
Anticoagulation carries the risk of hemorrhage, especially in patients with concomitant complications, such as cortical venous infarction, necrosis of intracavernous portions of the carotid artery, or cerebral or intraorbital hemorrhages.[50] Close monitoring of the activated partial thromboplastin time (aPTT) is required during therapy. The aPTT should be maintained between 1.5 to 2.0 times normal.[15] If a patient is considered suitable for anticoagulation but deteriorates despite this therapy, they may be considered for endovascular therapy.[87] [88] [89] Although endovascular treatment is increasingly being used to treat patients with cerebral venous thrombosis, this treatment is not routinely recommended in all patients.[90] This therapy is usually reserved for progressive, aseptic CST and carries with it the risks of intracranial hemorrhage and stroke and the inability to recanalize.		
dural venous thrombosis	**short term**	**low**
Thrombosis can extend to the other dural venous sinuses, depending on the site and extent of involvement.[57]		
carotid thrombosis	**short term**	**low**
Leads to stroke.		
hemiparesis	**short term**	**low**
Can occur secondary to carotid thrombosis with subsequent stroke.		

Complications	Timeframe	Likelihood
dysphasia	**short term**	**low**
Can occur secondary to carotid thrombosis with subsequent stroke.		
cranial nerve deficits	**long term**	**high**
Up to 30% of survivors will be left with cranial nerve deficits, although these will improve over a period of months.[2] These affect the abducens and oculomotor nerves predominantly, although trochlear, trigeminal, and optic nerves may be affected permanently.[1] [50]		
blindness	**long term**	**low**
Reported to occur in 9% of septic cavernous sinus thrombosis cases.[4] The cause is speculated to be: pressure on the retinal artery or vein, arteritis of the internal carotid artery, emboli to the retinal artery or optic nerve neuropathy.[98] [99]		
intracranial abscess (e.g., subdural empyema or intraparenchymal abscess)	**variable**	**low**
The presentation of intracranial abscesses have been reported to occur up to 8 months after cavernous sinus thrombosis (CST).[57] [96] Choice of antibiotics in the presence of brain abscess is usually meropenem alone. Duration of treatment in the presence of such a complication should be extended to at least 6 to 8 weeks.[1] Aspiration of such abscesses is usually required. Craniotomy, with excision of the abscess, may also be needed if the patient's condition deteriorates.[96]		
pituitary insufficiency	**variable**	**low**
Can occur acutely, requiring immediate treatment with corticosteroids, and may be life-threatening.[91] If suspected, then replacement should be started immediately while waiting for laboratory confirmation.[91] Has been reported to occur as a long-term complication at 4 years after diagnosis of CST, with manifestations of hypothyroidism and hypogonadism.[100]		
residual facial swelling and discoloration	**variable**	**low**
Occurs as a complication of the disease.		

Prognosis

The overall mortality rate associated with septic cavernous sinus thrombosis (CST) has decreased from 80% to 100% in the pre-antibiotic era to 20% to 30% since 1940.[1]

FOLLOW UP

Once the acute phase has resolved, recovery is gradual. Up to 30% have serious sequelae, including:[10] [15][22][50] [92]

- Residual cranial nerve (CN) paresis, affecting CN III and CN IV predominantly
- Blindness
- Hemiparesis
- Dysphasia
- Pituitary insufficiency
- Residual facial swelling and discoloration.

Morbidity and mortality are especially high when diagnosis and treatment are delayed.[15] Early management of the primary source of infection, such as endoscopic sinus surgery for sphenoid sinusitis, is crucial in reducing morbidity and mortality.[13] There are limited data distinguishing outcomes in septic versus aseptic CST, although, generally, it is thought that outcomes are better in aseptic disease.

Diagnostic guidelines

International

ACR appropriateness criteria: cerebrovascular diseases-stroke and stroke-related conditions (https://www.acr.org/Clinical-Resources/Clinical-Tools-and-Reference/Appropriateness-Criteria) [54]

Published by: American College of Radiology **Last published:** 2023

ACR appropriateness criteria: headache (https://www.acr.org/Clinical-Resources/Clinical-Tools-and-Reference/Appropriateness-Criteria) [56]

Published by: American College of Radiology **Last published:** 2022

ACR appropriateness criteria: orbits, vision and visual loss (https://www.acr.org/Clinical-Resources/Clinical-Tools-and-Reference/Appropriateness-Criteria) [58]

Published by: American College of Radiology **Last published:** 2017

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Images

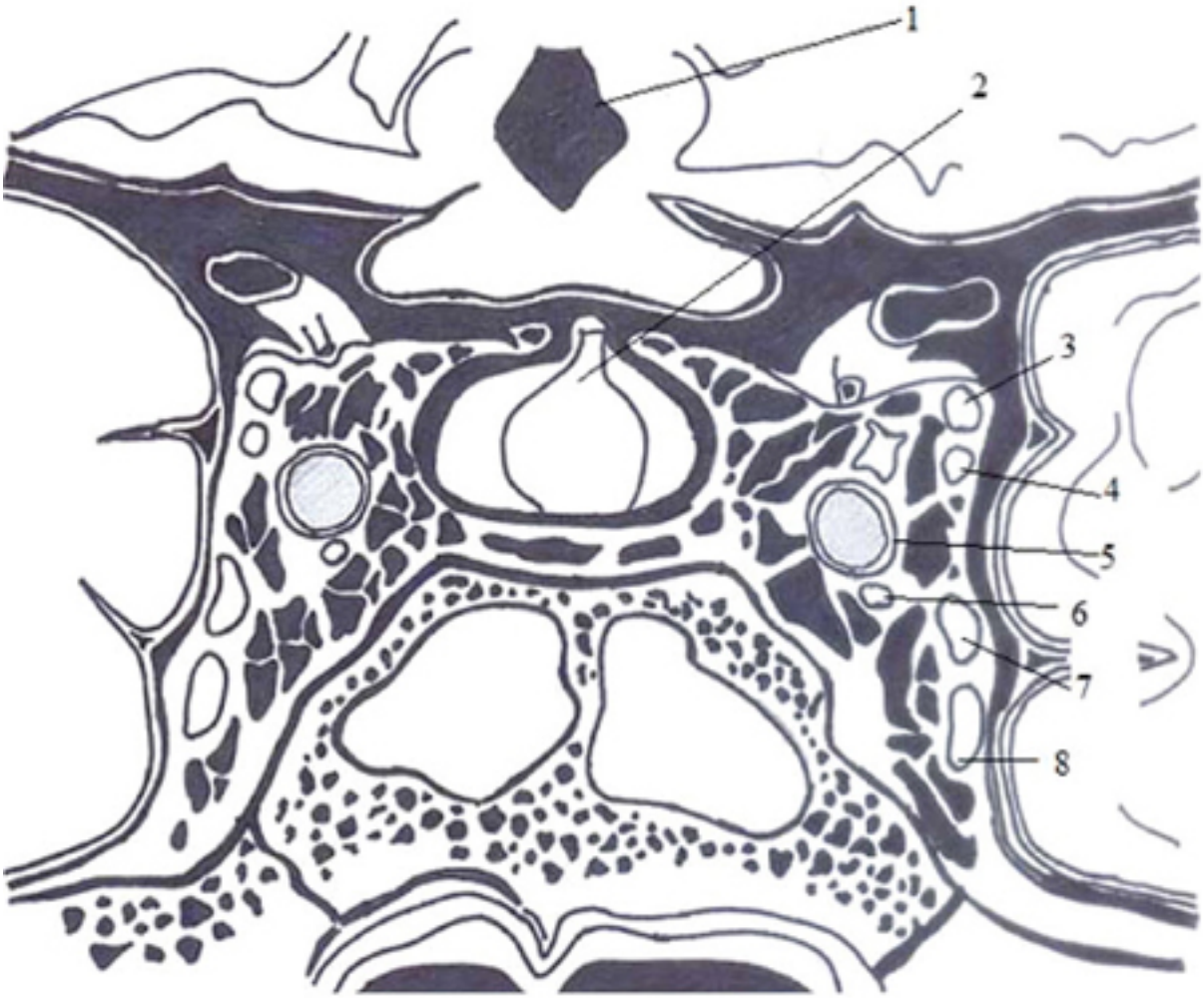

Figure 1: Anatomy of the cavernous sinus: (1) third ventricle, (2) pituitary gland, (3) oculomotor nerve, (4) trochlear nerve, (5) internal carotid artery, (6) abducens nerve, (7) ophthalmic branch of the trigeminal nerve, and (8) maxillary branch of the trigeminal nerve

Visvanathan V, et al. Reminder of important clinical lesson: ocular manifestations of cavernous sinus thrombosis. BMJ Case Rep. 2010; doi:10.1136. Used with permission

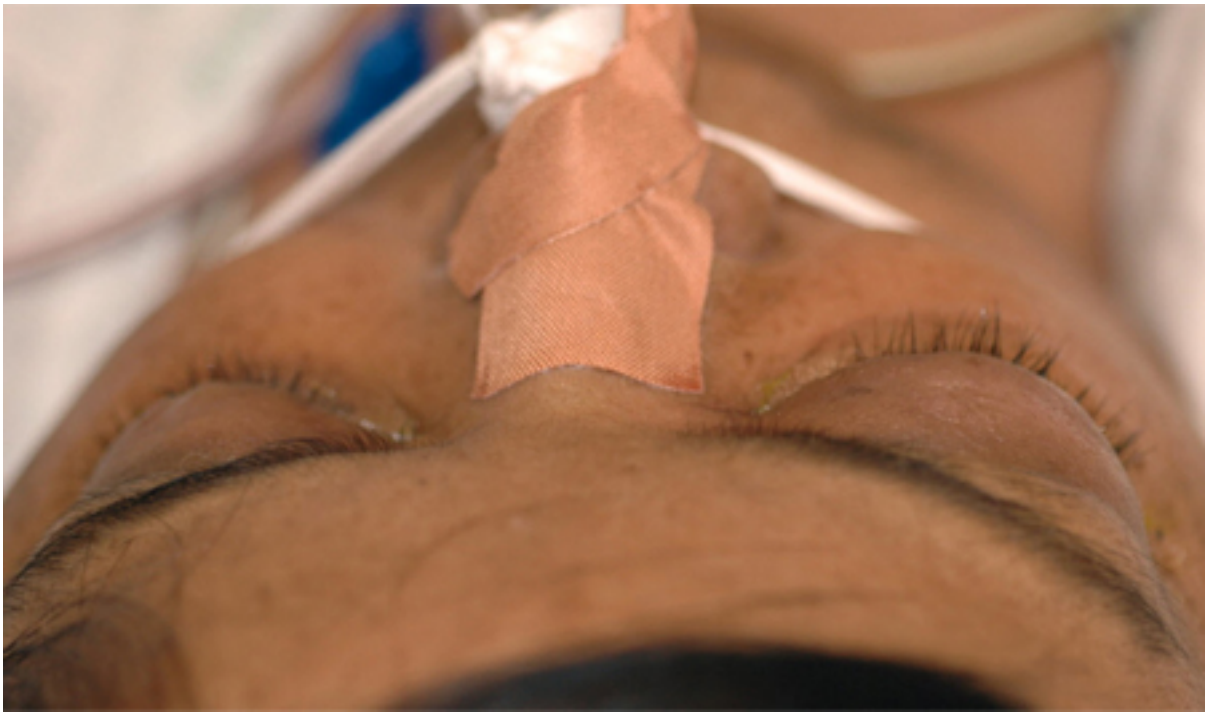

Figure 2: Proptosis of the right eye in a patient with cavernous sinus thrombosis secondary to dental infection

Jones RG, Arnold B. Sudden onset proptosis secondary to cavernous sinus thrombosis from underlying mandibular dental infection. BMJ Case Rep. 2009;2009. pii: bcr03.2009.1671. Used with permission

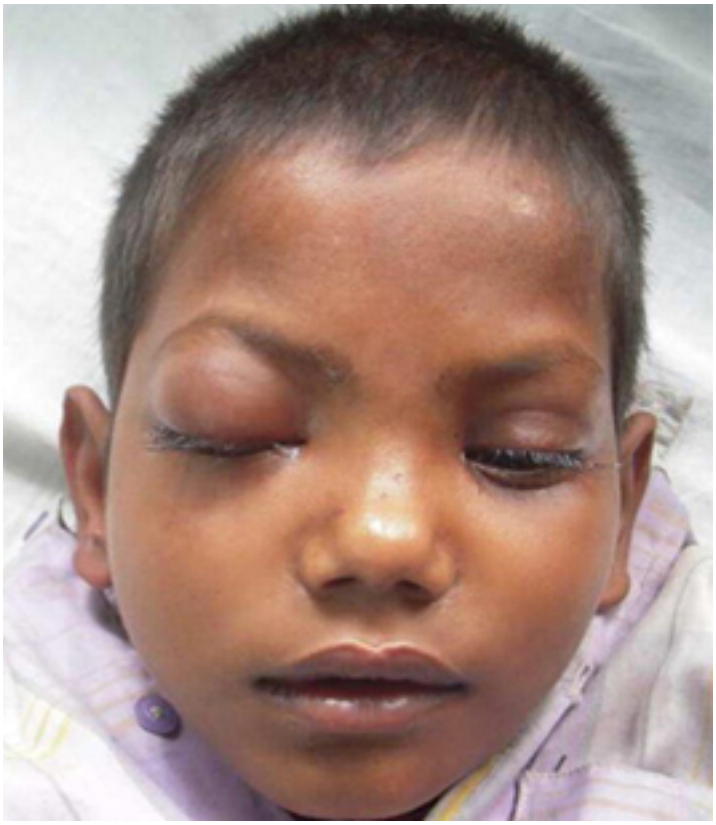

Figure 3: Patient with bilateral cavernous sinus thrombosis. Note the bilateral proptosis, which is more marked in the right eye

Vidhate MR, et al. Bilateral cavernous sinus syndrome and bilateral cerebral infarcts: a rare combination after wasp sting. J Neurol Sci. 2011;301:104-106. Used with permission

Ocular manifestatations of cavernous sinus thrombosis and their underlying pathology.

Anatomic region	Signs	Pathology/involved structure
Eyelids and Orbit	Ptosis	Edema of upper eye lid
		+/- sympathetic plexus
		involvement through III CN
	Chemosis	Thrombosis of superior & inferior ophthalmic veins
	Proptosis	
	Orbital cellulitis	
	Peri-orbital sensory loss	Involvement of V CN (ophthalmic/trigeminal divisions)
Cornea	↓Corneal reflex	V CN involvement (ophthalmic division)
	Corneal ulcers	Corneal exposure due to inability to close eyes.
Pupils	↓or absent Pupillary response	Raised intraocular pressure or optic neuropathy causing afferent pupillary defect
	Dialated	III CN (parasympathetic plexus)
	Small	sympathetic plexus involvement (III CN) affecting iris and ciliary apparatus
EOM Movement	Lateral rectus palsy	VI CN
	Complete Ophthalmoplegia	Dysfunction of CN III, IV & VI
Visual acuity	↓visual acuity or blindness	Central retinal artery/vein occlusion secondary to ICA arteritis, septic emboli or ischemic optic neuropathy

↓Decreased, ICA internal carotid artery, CN cranial nerve, EOM extraocular muscle

Figure 4: Ocular manifestations of cavernous sinus thrombosis and their underlying pathology

Visvanathan V, et al. Reminder of important clinical lesson: ocular manifestations of cavernous sinus thrombosis. BMJ Case Rep. 2010; doi:10.1136. Used with permission

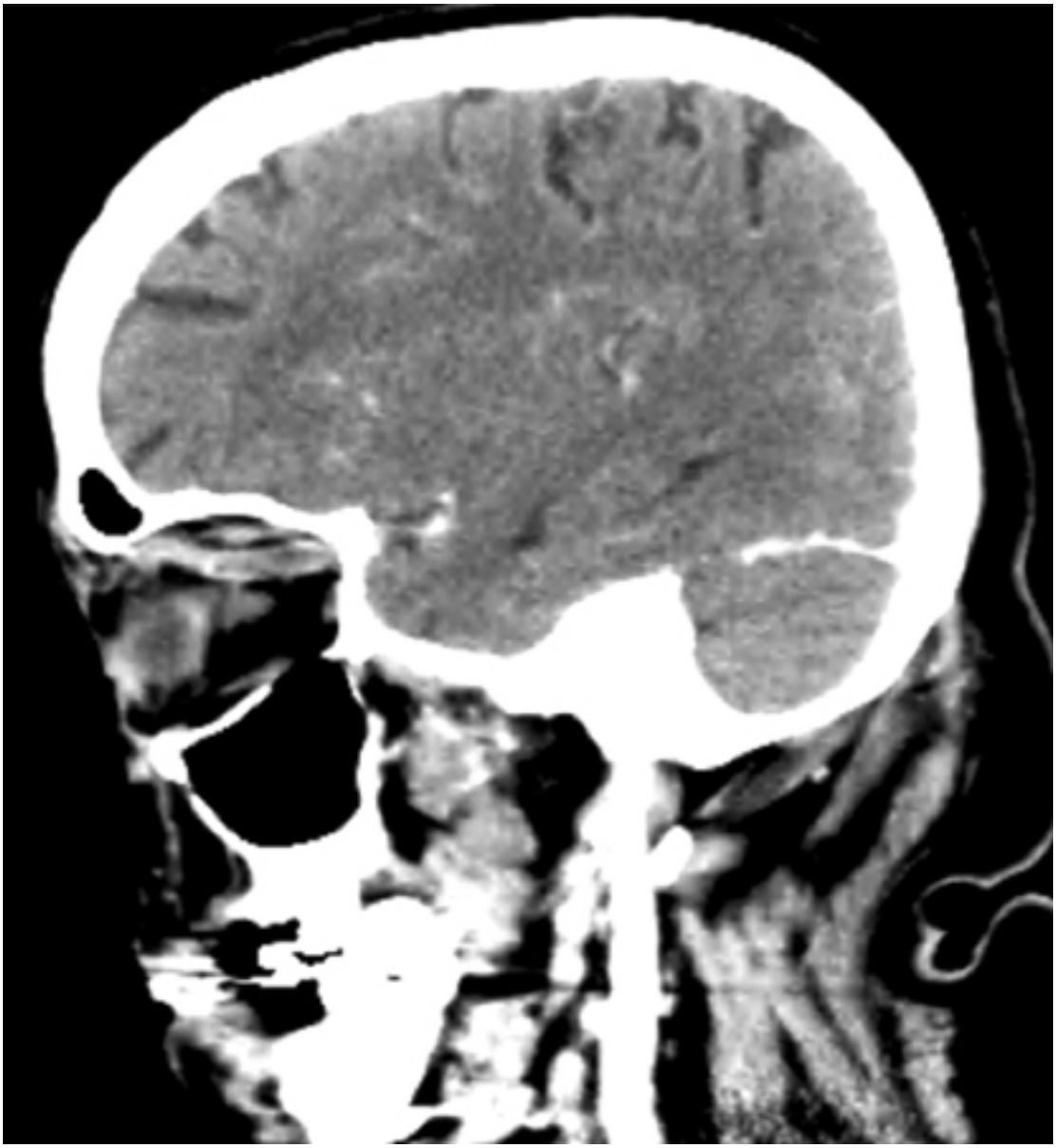

Figure 5: Sagittal CT scan of the head demonstrating an enlarged, tubular right superior ophthalmic vein

Jones RG, Arnold B. Sudden onset proptosis secondary to cavernous sinus thrombosis from underlying mandibular dental infection. BMJ Case Rep. 2009;2009. pii: bcr03.2009.1671. Used with permission

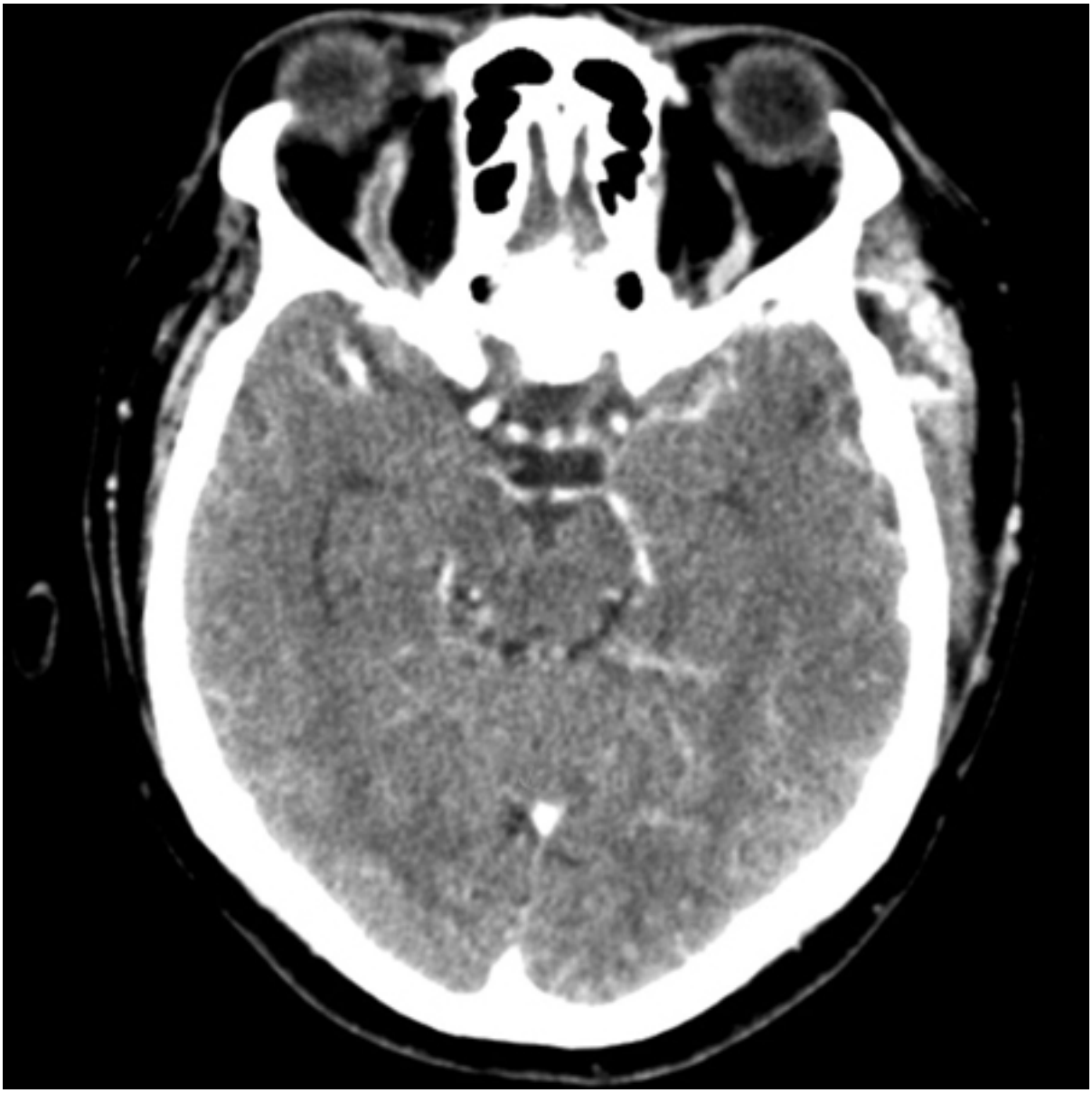

Figure 6: Postcontrast venous phase CT scan of the head (axial view) showing an enlarged 'S'-shaped right superior ophthalmic vein with associated proptosis

Jones RG, Arnold B. Sudden onset proptosis secondary to cavernous sinus thrombosis from underlying mandibular dental infection. BMJ Case Rep. 2009;2009. pii: bcr03.2009.1671. Used with permission

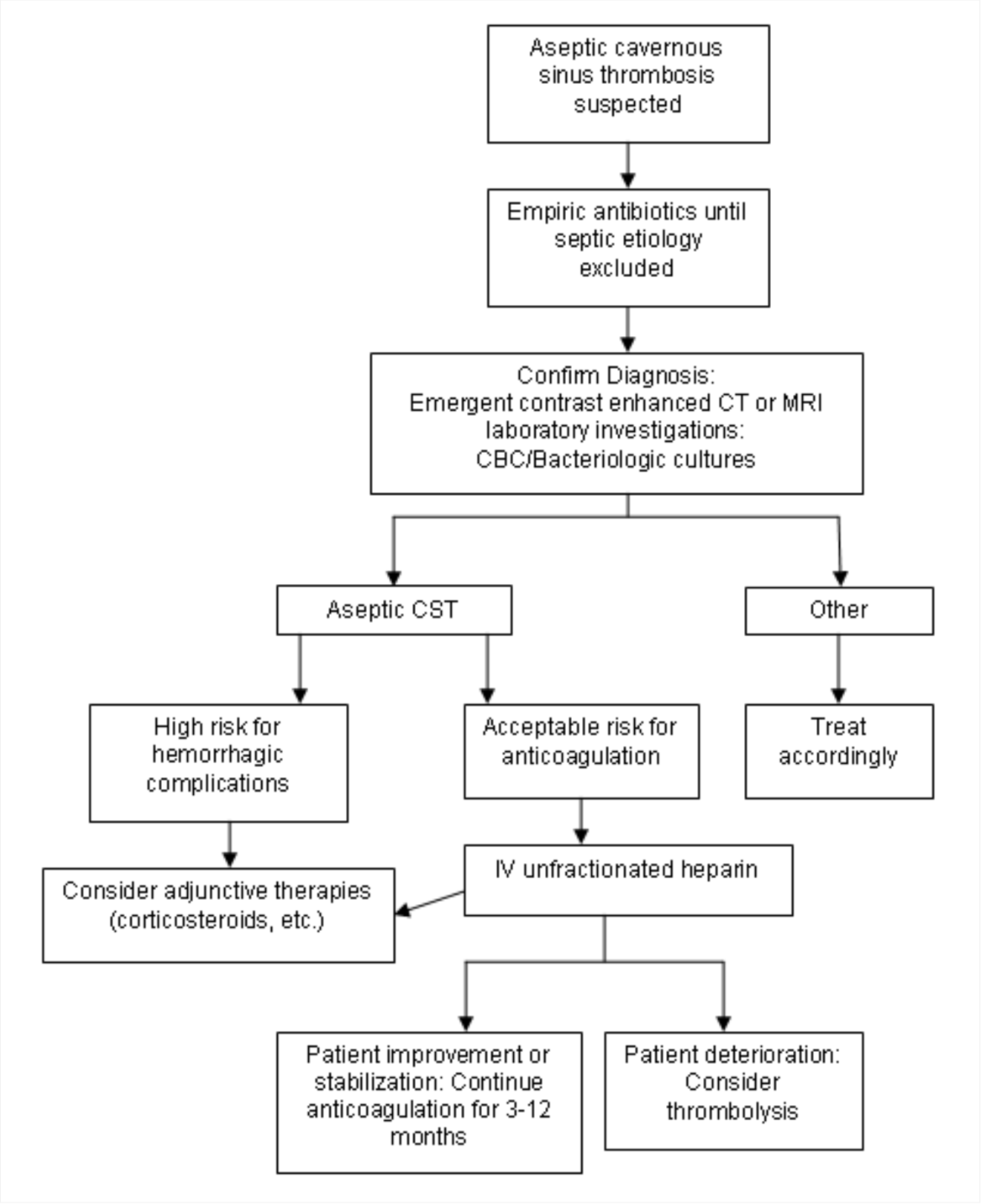

Figure 7: Treatment of aseptic cavernous sinus thrombosis (CST)

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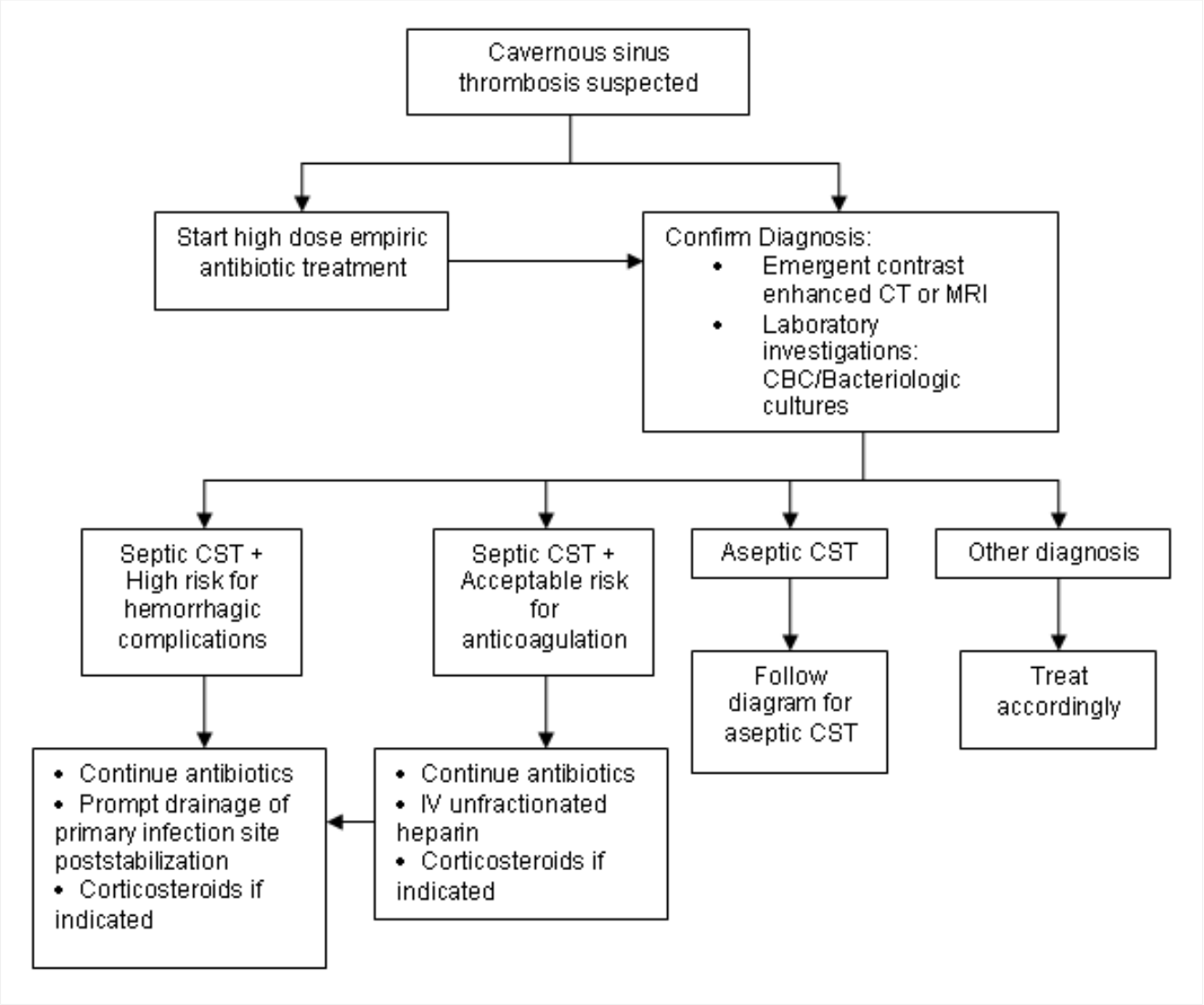

Figure 8: Treatment of septic cavernous sinus thrombosis (CST)

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