

Neonatal Cerebral Sinovenous Thrombosis (CSVT)





Implementation Date: October 15, 2018



#### Clinical Practice Guideline: Neonatal Cerebral Sinovenous Thrombosis (CSVT)

# Points of emphasis/Primary changes in practice:

- 1- Facilitating better understanding of the risk factors for neonatal CSVT.
- 2- Establishing a Clinical Practice Guideline for neonatal CSVT.
- 3- Implement a standardized algorithm to evaluate neonates with CSVT.

#### Rationale for change:

Cerebral venous sinus thrombosis (CSVT) in the neonate, increasing recognized in recently years, is an important variety of neonatal stroke. Although CSVT is relatively uncommon, it can lead to significant adverse neurological outcomes. Recently the diagnosis of CSVT has increased, largely because of improved awareness and advanced neuroimaging. Neonatal CSVT has a complex pathogenesis, often resulting from a combination of risk factors. Moreover, the approach to treatment varies worldwide, in part because of a lack of consensus on optimal timing and type of intervention. This clinical practice guideline is designed to facilitate prompt diagnosis, full characterization of the brain abnormalities, and best approach to management.

<u>Questions</u>? Please contact: Director of Neonatal Neurocritical Care, Department of Pediatric Newborn Medicine, BWH.



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This is a clinical practice guideline. While the guideline is useful in approaching the newborn with CSVT in the intensive care unit, clinical judgment and / or new evidence may favor an alternative plan of care, the rationale for which should be documented in the medical record.

# I. Purpose

The purpose of this clinical practice guidelines is to establish standard practices when approaching, evaluating, investigating, monitoring, and managing neonates with CSVT.

II. All CPGs will rely on the <u>NICU Nursing Standards of Care</u>.

# III. Patient population

This protocol applies to both term and preterm infants admitted to the BWH Neonatal Intensive Care Unit and the Well Newborn Nursery who are suspected of having CSVT. The scope of this guideline includes the identification, evaluation, monitoring, diagnosis, treatment and care of affected neonates and their families.



#### IV. Guideline

#### **Incidence**

The incidence of CSVT in neonates is 0.6-15 per 100,000 newborns per year, which is higher than the incidence in the childhood period (0.67 per 100,00 children per year). Although data are limited the incidence is considerably higher in preterm than term infants. Among different classes of perinatal stroke, CSVT is less common than arterial ischemic stroke (AIS). The reported incidence of CSVT is probably underestimated due to various reasons: non-specific clinical presentations, lack of clinician awareness, and the relative difficulty of radiological diagnosis in the neonate.

# Pathophysiology:

A venous clot leads to occlusion and impairment of drainage of cerebral veins. The result is, increased venous pressure, diminished capillary blood flow, vasogenic edema, and infarction, usually hemorrhagic in nature. Thrombosis can be diagnosed by imaging with or without parenchymal involvement.<sup>2,3</sup>

**Risk factors:** The risk factors for CSVT overlap with those for neonatal AIS. The following factors are reported most commonly.<sup>4-8</sup>

#### Maternal/ Neonatal factors:

- Primiparity
- Multiple births
- Gestational diabetes
- Pre-eclampsia
- Preterm birth
- Chorioamnionitis
- Complicated delivery (vacuums, forceps), meconium aspiration, intubation at birth, hypoxia, acidosis, and asphyxia
- Acute systemic illness: meningitis, sepsis and dehydration
- Congenital heart disease
- ECMO: infants who require ECMO are at risk of CSVT due to retrograde thrombosis following and occlusion of right jugular flow.<sup>6</sup>



#### **Prothrombotic factors:**

- Abnormal levels of prothrombotic factors are found in 10-20% of infants with CSVT but the abnormalities are usually minor and occur in the context of other risk factors.
- Recent studies investigating thrombophilia in neonatal CSVT do not predict recurrence.<sup>9</sup>
  - A population-based, prospective case-control study showed that prothrombotic abnormalities were not significantly different between CSVT cases and controls at 12 months.<sup>10</sup>

#### Other risk factors:

- Male sex has been identified as a risk factor.<sup>7,11</sup>
- Mechanical compression during intrapartum events and of the occipital bone in the supine position also has been associated with CSVT. (11)

#### V. Guideline

The neonate suspected of having a CSVT should be evaluated with neuroimaging to make the diagnosis prior to detailed assessment of risk factors and formulation of treatment.

#### **Clinical Presentation:**

Suspicion of neonatal stroke could arise from:

- 1. **Incidental neuroimaging** including routine head sonogram in NICU, and MRI for other reasons e.g., term equivalent MRI, before cardiac surgery, evaluation of encephalopathy.
- 2. **Intraventricular hemorrhage** in term infants or hemorrhagic infarction, especially involving parasagittal cerebrum, thalamus or basal ganglia should arouse suspicion of CSVT.<sup>12</sup>
- 3. Clinical manifestations: 4,7,13
  - Seizures are the most common presentation (60-70%) of neonatal CSVT.
     Generalized and focal seizures are both common in CSVT, which is different than neonatal seizure with AIS, which are predominantly focal.
     Also, seizures with neonatal CSVT occur slightly later (later in first week or beyond) than with AIS (first day).



- Encephalopathy which can mimic hypoxic ischemic encephalopathy, is another common presentation.
- Respiratory distress, apnea, tone abnormalities, and feeding difficulties have also been reported, especially in preterm infants.

#### 4. Other features:

Focal EEG abnormality, unexplained thrombocytopenia<sup>14</sup>

**Diagnosis:** Neuroimaging is mandatory to diagnose neonatal CSVT. The choices of neuroimaging are:

- Ultrasound: the presence of intraventricular hemorrhage, particularly when combined with thalamic hemorrhage, suggest the presence of CSVT. Color flow Doppler ultrasound may be used to assist in the diagnostic process by demonstrating decreased or absent flow in venous sinuses and major cerebral veins.<sup>15</sup>
- **MRI**: is the modality of choice to detect neonatal CSVT by demonstrating thrombus and parenchymal involvement.
  - o Diffusion-Weighted imaging (DWI) combined with apparent diffusion coefficient (ADC) mapping detects infarcts within minutes of occurrence.
  - o Routine sequences, T1-weighted and T-2 weighted imaging, are useful for evaluation of blood products and edema.
  - Susceptibility-weighted imaging (SWI) sequences are most sensitive to detect blood products and hemorrhagic transformation.
- Magnetic resonance venography (MRV) (time-of-flight) is the gold standard diagnostic approach to detect thrombus in the cerebral veins and sinuses.<sup>16</sup>
   Optimal detail concerning clot extent can be obtained with volumetric T1 weighted postcontrast imaging.

# Assessment and monitoring:

- Perinatal history: primiparity, maternal conditions (infertility, multiple births, gestational diabetes), drug exposure, smoking, history of recurrent fetal loss, preeclampsia, chorioamnionitis
- Delivery complications: fetal distress, emergency cesarean section, instrumental delivery
- Placenta examination: contact delivery obstetrician to send placental pathology



- Neonatal examination focus on visceral and limb thrombosis, sepsis, dehydration, congenital heart disease
- Neurological examination: encephalopathy, seizures
- Cardiorespiratory monitoring
  - o HR, BP, RR, O<sub>2</sub> sat
- EEG monitoring: <u>EEG Neuro-monitoring per NICU CPG</u>
- Consider NIRS monitoring: Clinical NIRS in the NICU CPG
- Consult BCH Intensive Care Neurology Consult Service (if not already consulted.
- Consult BCH Stroke and Cerebrovascular Neurology Service (BCH pager 1659)
- Imaging: MRA/MRV Brain if not already done with Brain MRI
- Laboratory tests
  - o Inflammatory markers: CBC, ESR, CRP, vWF Ag
  - Infection: Blood culture, Consider LP, if suspicion of meningitis or positive blood culture. <u>NICU L.1 Assisting with Lumbar Puncture</u>
  - Extensive prothrombotic screening (Appendix 3) should be conducted in neonates with:
    - Evidence of systemic hypercoagulable states in neonates (e.g., more than one site of thrombosis)
    - Family history of hypercoagulability: These questions are the examples to ask:
      - ➤ Does any family member (first degree relative) have a history of early heart attack or stroke (before 50 year-old)?
      - Does any family member (first degree relative) have a history of deep vein thrombosis or pulmonary embolism?
      - Does the mother have a history of multiple (2 or more) miscarriages?

**Treatment:** supportive treatment with neuroprotection strategy

- Control seizures <u>Neonatal seizure protocol</u>
- Normalization of blood sugar, BP
- Optimize ventilation and oxygenation
- Avoid dehydration
- Treat sepsis and meningitis
- Avoid hypo and hyperthermia
- Early rehabilitation;
  - Consult NICU Physical Therapy and Occupational Therapy via EPICS orders tab



- Therapy would be acknowledged/ completed within 48 hours of infant assuming medical stability and prior infant to discharge
- Referral for early intervention services
- Referral to outpatient follow up Boston Children's Hospital (BCH) Stroke clinic
- Referral for outpatient follow up at BWH NICU Follow up Program by ordering in Epic (Discharge>Orders>Additional Outpatient Orders>Ambulatory Referral to BWH Center for Child Development) for developmental evaluation starting 2-4 weeks after discharge

# Anticoagulation therapy:

- A distinct tendency toward anticoagulation therapy has developed in recent years.
- There is consider variability of therapeutic practice around the world, in part due to lack of definitive evidence. A recent large study revealed that neonates in the United States were significantly less likely to receive antithrombotic treatment compared to those in Canada or Europe. 17-20
- Consult Hematologist if considering anticoagulation treatment
- CSVT: consider low molecular weight heparin (LMWH) or unfractionated heparin (UH) in neonates with severe thrombosis or clot propagation despite supportive treatment, but without intracerebral hemorrhage.<sup>21,22</sup>
- Clot propagation occur in 25-30% of cases; anticoagulation therapy reduces the rate to about 3%.
- Dosages of antithrombotic therapy (Enoxaparin) are provided in <u>BWH NICU</u> DAG.

# Prognosis and outcome:

- Recurrence rate is low (2%).9
- Propagation occurs in 25-30%.
- Death is more common than with AIS and may approach 10-20%, depending considerably on associated conditions.<sup>5,7,19</sup>
- There is limited literature describing outcomes: 60-80% of all infants have some neurological deficits; motor impairment occurs in approximately 50% of survivors; cognitive impairment is reported in 10-60%, and epilepsy in 30-40%.<sup>3,19</sup>



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# Appendix 1- Algorithm to document of neonatal CSVT

# **Incidental imaging finding:**

-IVH in term neonates with or w/o thalamic hemorrhage

# **Neurological signs**

- -Seizures in the absence of asphyxia
- -Unexplained encephalopathy
- -Apnea or respiratory difficulties without explanation
- -Asymmetric movement of limbs or asymmetry in resting posture
- -Abnormal tone, arousal, or state regulation
- -Abnormal feeding without explanation

#### Other indications

- -Focal EEG abnormality
- -Unexplained low platelet count





Neonatal stroke suspected



HUS (consider Doppler)
MRI brain
MRA / MRV brain

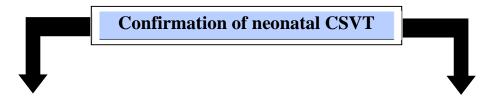


**Confirmation of neonatal CSVT** 





# Appendix 2- Algorithm for evaluation and treatment of neonatal cerebral sinovenous thrombosis (CSVT)



#### **Assess risk factors**

- -Antenatal history
- -Peripartum history and complications
- -Neonatal physical exam and neurological exam
- **Placenta exam**: contact delivery obstetrician to send placental pathology

# **Monitor:** HR, BP, RR, O<sub>2</sub> sat **Supportive treatment**

- -Normalization of temperature, glucose and lytes
- -Optimize ventilation and oxygenation
- -Avoid dehydration
- -Treat sepsis, meningitis
- -Consider monitor with NIRS

Consult BCH Intensive Care Neurology Service Consult BCH Stroke and Cerebrovascular Neurology Service (BCH pager 1659)

**EEG** monitoring

**Treatment of seizure** 

Consult NICU Physical Therapy and/or Occupational Therapy

# Diagnostic evaluation targeted to clinical etiology

- **-Infection**: blood culture, consider LP if suspect CNS infection or blood culture positive
- -Inflammatory markers: CBC, ESR, CRP, vWF
- **-Hypercoagulable state:** Prothrombotic screen as Appendix 3

#### **Anticoagulation therapy:**

- -Consider LMWH or UH in selected neonates with severe thrombophilic disorders, propagation of clot, and without large hemorrhage
- If considered, consult hematologist



# Appendix 3: Indications and Tests for Hypercoagulability State

# **A- Indications:**

Prethrombotic tests should be considered in neonates with:

- 1) Family history of hypercoagulability: These questions are the examples to ask:
  - -Does any family member (first degree relative) have a history of early heart attack or stroke (before 50 year-old)?
  - -Does any family member (first degree relative) have a history of deep vein thrombosis or pulmonary embolism?
  - -Does the mother have a history of multiple (2 or more) miscarriages?
- 2) Evidence of systemic hypercoagulable states (examples include: more than one site of thrombosis, extension of thrombosis1,35,42

#### **B- Tests:**

Plasma/Protein Based	DNA Based
Antiphospholipid antibodies	Factor V Leiden gene mutation*
Lupus anticoagulant*	Prothrombin gene mutation*
Anti-β2 glycoprotein 1 antibodies, IgG and	MTHFR mutation§
IgM**	
Anti-cardiolipin antibodies, IgG, IgA and IgM**	
Protein C functional assay*	
Protein S*	
Plasminogen*	
Serum homocysteine level <sup>[]</sup>	
Serum lipoprotein (a)**	
Fibrinogen*	
Factor VIIIC*	

<sup>\*</sup>Blue top Na citrate tube, 3 ml \*\*Gold top tube, plain, gel, 4 ml, 「Lavender top tube, EDTA, 4 ml on ice (minimum 0.4 ml), §Yellow top ACD B tube 10 ml (1 ml minimum in 3 ml ACD tube)



# **Appendix 4 - Early Rehabilitation Services:**

- Consult NICU Physical Therapy and/or Occupational Therapy via EPIC orders
- Rationale:
  - o Provide intervention during a "critical period" of development (1-2, 8)
    - Period of "activity-dependent plasticity" critical in the first few years of life, specifically the first 6 months when considering corticospinal tract development
    - Preserve normal function of descending motor pathways; progression from primarily bilateral projections from each hemisphere to spinal cord at term age to gradual, activity dependent, crossed projection in typically developing infants. Best functional outcome in infants who retain crossed projection of corticospinal tract from affected hemisphere.
  - Trained professionals monitoring trends in infant's development during inpatient admission. Detect abnormal findings on neurological exam and/or during General Movements Assessment
    - Abnormal findings on neurological examination at discharge predictive of one or more disabilities on long term follow up (8)
    - Early predictors include
      - MRI findings
      - "General Movements Assessment" specifically during period between 3-16 weeks (1-3)
- Therapy Based Approaches: (1-2, 4-8)
  - Limited research re: interventions in neonates and during the "silent period" where asymmetry of movement is not typically observed in infants < 3 months; majority of research re: constraint induced movement therapy (CIMT) and/or bimanual therapy interventions in infants > 3-6 months
  - o Promote activity of involved side/limbs while balancing preservation of normal activity level and development of non-involved side/limbs; potentially harmful to institute (CIMT) practices too early
  - o Manipulating infant's environment and integrating therapeutic activities into routine caregiving tasks
  - Parent education and involvement
  - Earlier onset of effective intervention assists with parent involvement and assist with prevention of risk factors leading to secondary morbidities
- Goals of Early Rehabilitation during NICU admission through infant's first 3 months:
  - o Encouragement of symmetry with functional tasks of neonate and newborn infant
    - Symmetrical resting head and neck posture and active neck rotation



- Symmetrical lower extremity resting posture and active kicking without hip adduction/ crossing
- Symmetrical upper extremity resting posture and active movement including self-soothing tasks
- Symmetrical rooting and active hand to mouth; sucking on bilateral hands/fingers
- Symmetrical visual tracking through full visual field laterally and vertically
- Consider modified constraint (with strategic swaddling) if asymmetry present but balancing providing plenty of opportunity for normal development and movement of non-involved side
- Ensure infant's state of arousal and state transitions are appropriate for gestational age
- Early counseling and family involvement in establishing therapeutic activities into routine care activities for long term.

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# Parent Information Sheet: Perinatal Stroke

#### What is a perinatal stroke?

A stroke is characterized as a disruption of cerebral vessels, and classified into two major categories: (1) hemorrhage, and (2) ischemic. Ischemic strokes are far more common, and caused by an obstruction within the blood vessels preventing blood flow to the brain. What differentiates a perinatal stroke from other types of stoke is timing. Perinatal strokes can occur while the baby is in the uterus, during delivery, or within weeks after birth.

# Can babies have stroke? I thought it only happened in adults!

Unfortunately, yes. Stroke is quite common among babies, occuring in 1 in every 4000 babies. This rate is similar to one seen for large artery stroke in adults even though the symptoms and causes are markedly different.

#### Then what is the cause of stroke in babies?

It is hard to know for sure what causes. In fact, over half of the cases of perinatal strokes have unclear causes. What we do know is that there exists a combination of risk factors linked with perinatal stroke. These include: (1) maternal factors like smoking and infertility, (2) placental disorders, (3) fetal or neonatal complications such as infection.

#### What tests are done when a baby has a stroke?

Because the cause can be unclear, we have to perform many tests: (1) an MRI of the brain will be conducted to look for specific features of the brain injury, (2) a blood test could be done to check for possible causes, (3) an electroencephaogram (EEG) is performed to monitor seizures and brain function, and (4) in rare cases a spinal tap is needed.

#### What to expect after discharge?

Many babies who suffer from perinatal stroke experience little to no neurological deficits. However some babies might be risk for motor deficits, subsequent seizures or devlopmental delay. We will refer your baby to BWH NICU follow up clinic, Stroke clinic and Early intervention services as needed. Follow up providers will monitor your baby for any of the following symptoms: fisting of one hand, asymmetry of movement, favoring one side of body, delays in motor skills, weakness or tightness on one side of body. Parents and other family members are strongly encouraged to look for these symptoms as well, but it is important to note that the babies do not show hand preference until after 18 months.







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