

**PEDIATRIC NEWBORN
MEDICINE CLINICAL
PRACTICE GUIDELINES**

Perinatal Arterial Ischemic
Stroke (PAIS)



Implementation Date: October 15, 2018



Clinical Practice Guideline: Perinatal Arterial Ischemic Stroke (PAIS)

Points of emphasis/Primary changes in practice:

- 1- Facilitating better understanding of the risk factors of perinatal arterial ischemic stroke.
- 2- Establishing a Clinical Practice Guideline for perinatal arterial ischemic stroke.
- 3- Implement a standardized algorithm to evaluate neonates with PAIS.
- 4- Implement standardized algorithm for subacute management/treatment, inpatient therapy and long term follow up referrals.

Rationale for change:

Perinatal stroke is a common disorder that has been shown to affect 1 in 1600-5000 births. The incidence rate is 17 times higher than in children, and similar to the rate of large artery stroke observed in adults. However, the presentation and etiologies of perinatal stroke can differ remarkably from these two groups. Perinatal stroke is associated with several long-term morbidities such as hemiplegic cerebral palsy (CP), epilepsy, sensorimotor impairment, cognitive and language impairment.

The disease remains incompletely understood and over half of the cases of perinatal stroke remain unexplained. There are many well-documented risk factors for perinatal stroke. This clinical practice guideline is designed to evaluate these risk factors more systematically so that we can optimize eventual outcomes.

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



Clinical Guideline Name	Perinatal Arterial Ischemic Stroke (PAIS)
Effective Date	
Revised Date	
Contact Person	
Approved By	Clinical Practice Council 10/12/18 Department of Newborn Medicine 11/1/18 Department of Neonatal Nursing 11/1/18
Keywords	Perinatal stroke, Risk factors

This is a clinical practice guideline. While the guideline is useful in approaching the neonates with perinatal stroke 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 guideline is to establish standard practices when approaching, evaluating, investigating, monitoring, and managing neonates with perinatal arterial ischemic stroke (PAIS).

II. All CPGs will rely on the [NICU Nursing Standards of Care](#).

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 perinatal stroke. The scope of this guideline includes the identification, evaluation, monitoring, diagnosis, treatment and care of such neonates and their families.

IV. Guideline

Definition



Perinatal stroke is defined by a vascular event causing focal interruption of blood supply, occurring between 20 weeks of fetal life through the 28th postnatal day, and confirmed by neuroimaging or neuropathology.¹

Classification

Perinatal stroke can be classified as either hemorrhagic or ischemic. Ischemic stroke is further categorized by the site (artery or vein), and the timing of presentation (fetal, neonatal, and presumed perinatal stroke). This guideline focuses on arterial ischemic stroke (AIS).

- Fetal ischemic stroke is diagnosed before birth by using fetal imaging methods or in stillbirths on the basis of neuropathologic examination.
- Neonatal ischemic stroke is diagnosed by neuroimaging after birth and or before the 28th postnatal day (including both term and preterm infants).
- Presumed perinatal ischemic stroke is diagnosed in infants >28 days of age in whom it is presumed (but not proven) that the ischemic event occurred sometime between the 20th week of fetal life through the 28th postnatal day.

Incidence

- Population based studies have reported the incidence of neonatal ischemic stroke in term infants to be 2-4/10000 live births.^{2,3}
- A hospital based study reported that among preterms, the incidence of AIS was 7 per 1000 infants < 34 weeks gestational age and considerably higher than the observed incidence among term infants (0.25 per 1000 infants).⁴

Pathophysiology

- Though many recent studies have defined association between perinatal stroke and risk factors, the mechanistic relationships remain unclear.
- Combinations of risk factors (maternal, placental, neonatal and other miscellaneous conditions) increase the likelihood of perinatal AIS. A cohort study of 37 cases of AIS found that 60% had three or more risk factors compared to only 6% of controls.² Thus, the data suggest that the pathogenesis of perinatal AIS is very often multifactorial. (Table 1)

**Table 1. Major risk factors for neonatal arterial ischemic stroke⁵**

Source of risk factor	Risk factor
Maternal (prepartum)	Primiparous Infertility Smoking Intrauterine growth restriction Preeclampsia Thrombophilia
Maternal (peripartum)	Maternal fever Maternal infection Prolonged ruptured of membranes Intrapartum complications
Neonatal	Male Apgar score <7 (5 minutes) Prolonged resuscitation Hypoglycemia Early-onset sepsis/meningitis Congenital heart disease Vascular abnormality Thrombophilia
Placenta	Cord complication Chorioamnionitis Chronic villitis with obliterative fetal vasculopathy, thrombotic vasculopathy, small placenta

Antepartum maternal factors:

- Pregnancy itself is a natural prothrombotic state: levels protein S and activated protein C are low, and thrombin generation, and levels of protein C, von Willebrand factors, Factors VIII and V, and fibrinogen are all elevated.⁶
- Primiparity is identified in 30-75% of cases of perinatal AIS in term infants, but not in preterm infants. In one study of AIS, primiparity was strongly related to prolonged second stage of labor in a multivariate analysis.²
- Maternal conditions such as thyroid disease, diabetes mellitus and gestational diabetes mellitus are reported with increased frequency in mothers of infants



presenting with AIS. However, the few data are unable to clarify these associations.

- Infertility has been reported in 7-11% of cases and suggests a possible relationship to the use of ovarian stimulating drugs that may potentiate the prothrombotic state.^{2,7}
- Oligohydramnios and decreased fetal movements are associated with perinatal AIS.^{2,7}
- Intrauterine growth retardation (IUGR) increases the risk of perinatal AIS; IUGR is a multifactorial disorder that is associated with preeclampsia, thrombotic lesions in placenta, placental insufficiency and increased maternal thrombin formation.⁸

Intrapartum maternal factors:

- Pre-eclampsia has been identified as an independent risk factors and is associated with vascular endothelial disruption in placental vessels that can reduce uteroplacental blood flow.^{2,8}
- Chorioamnionitis and prolonged rupture of membranes are inflammatory conditions identified as risk factors in perinatal AIS.²
- Prolonged second stage of labor, cord abnormalities, and intervention during delivery (emergency caesarean section, forceps or vacuum extraction) are common among neonates with AIS. However, elective caesarean section rates are low among infants that suffer from perinatal AIS. The high rate of perinatal AIS among infants that experienced interventional deliveries implied that compromised infants are at risk of perinatal AIS, but the causative pathway is still largely undefined.²

Placental disorders:

- The placenta represents a potential source of emboli conveyed to the fetal brain via the patent ductus venosus, which bypasses the liver, and thence through the foramen ovale to reach the cerebral circulation during late fetal life. Placental abnormalities associated with perinatal AIS consist of placental thrombotic vasculopathy, infarction, chorioamnionitis, funisitis and chorioangiomas.^{6,7}
- Placental pathology abnormalities were found in 89% of cases with neonatal AIS compared with controls (62%) in a recent publication.⁹ Fetal vascular



malperfusion related to several villous abnormalities, inflammation in both maternal and fetal placental components, and large placenta with chorangiosis were found significantly among children with perinatal AIS compared with controls.

Fetal and neonatal risk factors:

- Low Apgar score (<7) at 5 minutes, and requirement for resuscitation at birth have been identified as independent risk factors for AIS, and imply that generalized hypoxia ischemia may play a role in the pathogenesis of perinatal AIS.^{1-3,10}
- Fetal distress including fetal heart rate abnormalities and meconium-stained amniotic fluid are both commonly documented in infant with perinatal AIS.
- Meningitis and early neonatal sepsis are associated with an increased risk of perinatal AIS. Infection triggers release of inflammatory cytokines which in turn, may cause direct endothelial injury and a prothrombotic state.^{11,12}
- Hypoglycemia has been linked to perinatal AIS. Mechanism may relate to associated perinatal asphyxia, impaired cerebrovascular autoregulation, and inflammatory, and pro-thrombotic effects. Involvement of the posterior cerebral artery distribution is common.¹¹
- Twin-twin transfusion syndrome (TTTS), abnormal FHR pattern, and hypoglycemia have been identified as an independent risk factors for perinatal stroke in preterm neonates.⁴

Prothrombotic risk factors:

- Many studies have documented that at least one thrombophilic or related genetic risk factor was found at greater frequency among neonates with perinatal AIS or their birth mothers as compare to normal controls. The thrombophilic and other genetic risk factors documented include: factor V Leiden mutation, homozygous methylenetetrahydrofolate reductase (MTHFR) mutation, factors II mutation, elevated lipoprotein (a), increased factor VIII, and protein C deficiency.^{7,13-16}
- Antiphospholipid antibodies (APA) have been found among neonates with perinatal stroke or their mothers. It has been hypothesized that anticardiolipin antibodies could induce thrombosis in the placenta and thereby emboli to the



fetal or neonatal brain, or that these IgG antibodies could cross the placenta and cause cerebral thrombosis in the neonate.

- Prothrombotic risk factors have been reported in both preterm and term infants.⁴
- Risk factors often recommended for screening are summarized in Table 1.^{7,13,16}
- Recent studies investigating thrombophilia in perinatal stroke do not predict recurrence.
 - A population-based, prospective, case-control study shows that prothrombotic abnormalities were not different between AIS cases and controls at 12 months.¹⁷
 - The prevalence of recurrent ischemic cerebrovascular events among neonates with stroke has been reported at 2.8%, and abnormal thrombophilia testing was not associated with recurrent stroke.¹⁸

Cardiac risk factors:

- Congenital heart disease, particularly with right-left communication, predisposes neonates to cerebral thromboembolism.
- Neonatal cardiac repair procedures, particularly balloon atrial septostomy, have been associated with stroke occurrence.
- Cardiomyopathy, valve disease, and arrhythmia can also cause thromboembolism.^{19,20}

Miscellaneous risk factors:

- Male sex has been reported to be as an independent risk factor for perinatal AIS, but this association has not been fully explained nor uniformly replicated.^{11,21}
- A family history of seizures or neurological diseases, although uncommon, conveys a statistically significant risks for perinatal AIS. The biological mechanism is uncertain.²¹

V. Guideline

The neonate suspected of having a stroke should be evaluated with neuroimaging to confirm the diagnosis prior going to assessment of various risk factors and formulation of specific treatment.

Clinical Presentation:

Suspicion of neonatal stroke should be aroused by:



1. **Incidental finding on neuroimaging**, including fetal MRI, routine head sonogram in NICU, and MRI for other reasons e.g. Term equivalent MRI, before cardiac surgery.
2. **Clinical manifestations:**
 - Seizures are the most common presentation of perinatal AIS (69-90%). Notably, seizures associated with AIS have focal features, and tend to occur after 12 hours of postnatal life, in contrast to more generalized features and earlier onset in hypoxic-ischemic encephalopathy.^{3,22,23} Moreover, infants with seizures and neonatal AIS are less likely to exhibit encephalopathy than infants with hypoxic-ischemic encephalopathy. Recent publications reported that both seizure occurrence (OR 2.8, 95%CI 1.3-5.8), and presence of recurrent or prolonged seizures (OR 4.7, 95%CI 1.7-13) increased the risk of later epilepsy. Thus, prompt and appropriate seizure control can improve outcomes.^{24,25}
 - Encephalopathy, apnea, tone abnormalities, and asymmetric movement of limbs are other potential neurological presentations.^{3,22} Moreover, a number of newborns who presented with moderate encephalopathy and were therapeutically cooled, were found to have focal strokes on post-cooling studies.^{18,26}
 - Preterm infants with AIS are usually asymptomatic and diagnosed by routine head ultrasound. However, respiratory and feeding difficulties have often been reported in preterm infants with stroke.²⁷
3. **Other indicators:**
 - Focal EEG abnormality²⁸

Diagnosis:

Neuroimaging is mandatory to identify neonatal stroke. The choices of neuroimaging are:

- **Ultrasound:** is an easily accessible bedside tool. However, it is operator dependent and only moderately sensitivity in detection of acute ischemic stroke within the first 24 hours of occurrence. Ultrasound detects only 68% of AIS in the first three days of life and 87% between 4-10 days of stroke; and small areas of brain injury or posterior circulation infarcts are generally undetectable.²⁹



- **CT scan:** is a rapid procedure that does not require sedation. However, X-irradiation exposure occurs with CT and should be avoided in neonates.
- **MRI:** is the modality of choice to detect neonatal stroke. Similar to its use at later ages, the excellent anatomic resolution, high sensitivity for detection of acute ischemic infarcts, and lack of radiation exposure are major advantages.³⁰
 - Diffusion-Weighted imaging (DWI), combined with apparent diffusion coefficient (ADC) mapping, detects arterial infarcts within minutes of occurrence.
 - Routine sequences, such as T1-weighted and T2-weighted imaging, are useful for evaluation of blood products and edema.
 - Susceptibility-weighted imaging (SWI) sequences are most sensitive for detection of blood products and hemorrhagic transformation.
 - Magnetic resonance angiography (MRA) of the brain is often included in imaging of neonatal stroke.³¹ This technique is helpful to detect vascular stenosis, occlusion, or arteriopathy.

Assessment and monitoring:

- Prenatal and perinatal history: maternal conditions (infertility, gestational diabetes mellitus), drug exposure, smoking, history of recurrent fetal loss, pre-eclampsia, IUGR, primiparity, fever, chorioamnionitis, PROM
- Delivery complications: fetal distress, emergency caesarean section, instrumental delivery, depressed Apgar score, need for resuscitation
- Placenta examination: contact obstetrician to send placental pathology
- Neonatal examination: emphasis on cardiovascular system (e.g., congenital heart disease), visceral and limb thromboses, sepsis, meningitis, and hypoglycemia
- Neurological examination
- Cardiorespiratory monitoring
 - HR, BP, RR, O₂ sat
- EEG monitoring: [EEG Neuro-monitoring per NICU CPG](#)
- 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 if not already done with Brain MRI
- **Laboratory tests**
 - Inflammatory markers: CBC, ESR, CRP, vWF Ag



- Infection: Blood culture, Consider LP, if suspicion of meningitis or positive blood culture [NICU L.1 Assisting with Lumbar Puncture](#)
- **Consult Cardiology:** consider echocardiogram
- Extensive prothrombotic screening (**Appendix-3**) should be conducted among 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 strategy³²

- Control seizures [Neonatal seizure protocol](#)
- Normalization of blood sugar, BP
- Optimize ventilation and oxygenation
- Treat sepsis, meningitis
- 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:

- Data are lacking to support prophylactic treatment in neonatal stroke
- **Consult Hematologist** if consider anticoagulation treatment
- The current recommendation is anticoagulation treatment in proven cardiac embolism, recurrent AIS, or prothrombotic state.^{33,34}



- Dosages of antithrombotic therapy (Enoxaparin) are provided in [BWH NICU DAG](#).³⁵

Prognosis and outcome:

- Recurrence rate is low (2%).³⁶
- Death is a rare outcome (below 5%) and often associated with other comorbidities such as sepsis, complex congenital heart disease.³⁷
- Long term outcome
 - Cerebral palsy (CP): neonatal ischemic stroke resulted in hemiparesis in approximately 25-35% of cases. Risk of hemiparesis is higher if distribution of the stem of the middle cerebral artery is affected or if involvement of the ipsilateral hemisphere is also present.^{3,22,38}
 - Epilepsy occurs subsequently in 15-45%. Although uncommon, occurrence of infantile spasms is a strong predictor of the poor outcome.^{7,39} Prolonged or recurrent seizures at presentation with stroke early in life significantly increase the risk of subsequent epilepsy; a 5 fold-increased risk is associated with each additional 10 minutes of the acute longest seizures. Occurrence of more than 10 neonatal seizures increases the risk of subsequent epilepsy 30-fold.^{24,25}
 - Cognitive function at school age is impaired after unilateral infarctions in approximately 70%, often emerging only in childhood.⁴⁰
 - Behavioral disorders occur in approximately 10%.²²
 - Language delay is noted approximately 50% at age 7 years.⁴¹



References:

1. Raju TN, Nelson KB, Ferriero D, Lynch JK, Participants N-NPSW. Ischemic perinatal stroke: summary of a workshop sponsored by the National Institute of Child Health and Human Development and the National Institute of Neurological Disorders and Stroke. *Pediatrics*. 2007;120(3):609-616.
2. Lee J, Croen LA, Backstrand KH, et al. Maternal and infant characteristics associated with perinatal arterial stroke in the infant. *JAMA*. 2005;293(6):723-729.
3. Laugesaar R, Kolk A, Tomberg T, et al. Acutely and retrospectively diagnosed perinatal stroke: a population-based study. *Stroke*. 2007;38(8):2234-2240.
4. Benders MJ, Groenendaal F, Uiterwaal CS, et al. Maternal and infant characteristics associated with perinatal arterial stroke in the preterm infant. *Stroke*. 2007;38(6):1759-1765.
5. Volpe JJ, Inder TE, Darras BT. *Volpe's Neurology of the Newborn*. Elsevier; 2017.
6. Cheong JL, Cowan FM. Neonatal arterial ischaemic stroke: obstetric issues. *Semin Fetal Neonatal Med*. 2009;14(5):267-271.
7. Curry CJ, Bhullar S, Holmes J, Delozier CD, Roeder ER, Hutchison HT. Risk Factors for Perinatal Arterial Stroke: A Study of 60 Mother-Child Pairs. *Pediatric Neurology*. 2007;37(2):99-107.
8. Wu YW, March WM, Croen LA, Grether JK, Escobar GJ, Newman TB. Perinatal stroke in children with motor impairment: a population-based study. *Pediatrics*. 2004;114(3):612-619.
9. Bernson-Leung ME, Boyd TK, Meserve EE, et al. Placental Pathology in Neonatal Stroke: A Retrospective Case-Control Study. *J Pediatr*. 2018.
10. Michoulas A, Basheer SN, Roland EH, Poskitt K, Miller S, Hill A. The role of hypoxia-ischemia in term newborns with arterial stroke. *Pediatr Neurol*. 2011;44(4):254-258.
11. Harteman JC, Groenendaal F, Kwee A, Welsing PM, Benders MJ, de Vries LS. Risk factors for perinatal arterial ischaemic stroke in full-term infants: a case-control study. *Arch Dis Child Fetal Neonatal Ed*. 2012;97(6):F411-416.
12. Fitzgerald KC, Golomb MR. Neonatal arterial ischemic stroke and sinovenous thrombosis associated with meningitis. *J Child Neurol*. 2007;22(7):818-822.
13. Simchen MJ, Goldstein G, Lubetsky A, Strauss T, Schiff E, Kenet G. Factor v Leiden and antiphospholipid antibodies in either mothers or infants increase the risk for perinatal arterial ischemic stroke. *Stroke*. 2009;40(1):65-70.
14. Suppiej A, Franzoi M, Gentilomo C, et al. High prevalence of inherited thrombophilia in 'presumed peri-neonatal' ischemic stroke. *Eur J Haematol*. 2008;80(1):71-75.
15. Mercuri E, Cowan F, Gupte G, et al. Prothrombotic disorders and abnormal neurodevelopmental outcome in infants with neonatal cerebral infarction. *Pediatrics*. 2001;107(6):1400-1404.
16. Gunther G, Junker R, Strater R, et al. Symptomatic ischemic stroke in full-term neonates : role of acquired and genetic prothrombotic risk factors. *Stroke*. 2000;31(10):2437-2441.
17. Curtis C, Mineyko A, Massicotte P, et al. Thrombophilia risk is not increased in children after perinatal stroke. *Blood*. 2017;129(20):2793-2800.
18. Lehman LL, Beaute J, Kapur K, et al. Workup for Perinatal Stroke Does Not Predict Recurrence. *Stroke*. 2017;48(8):2078-2083.



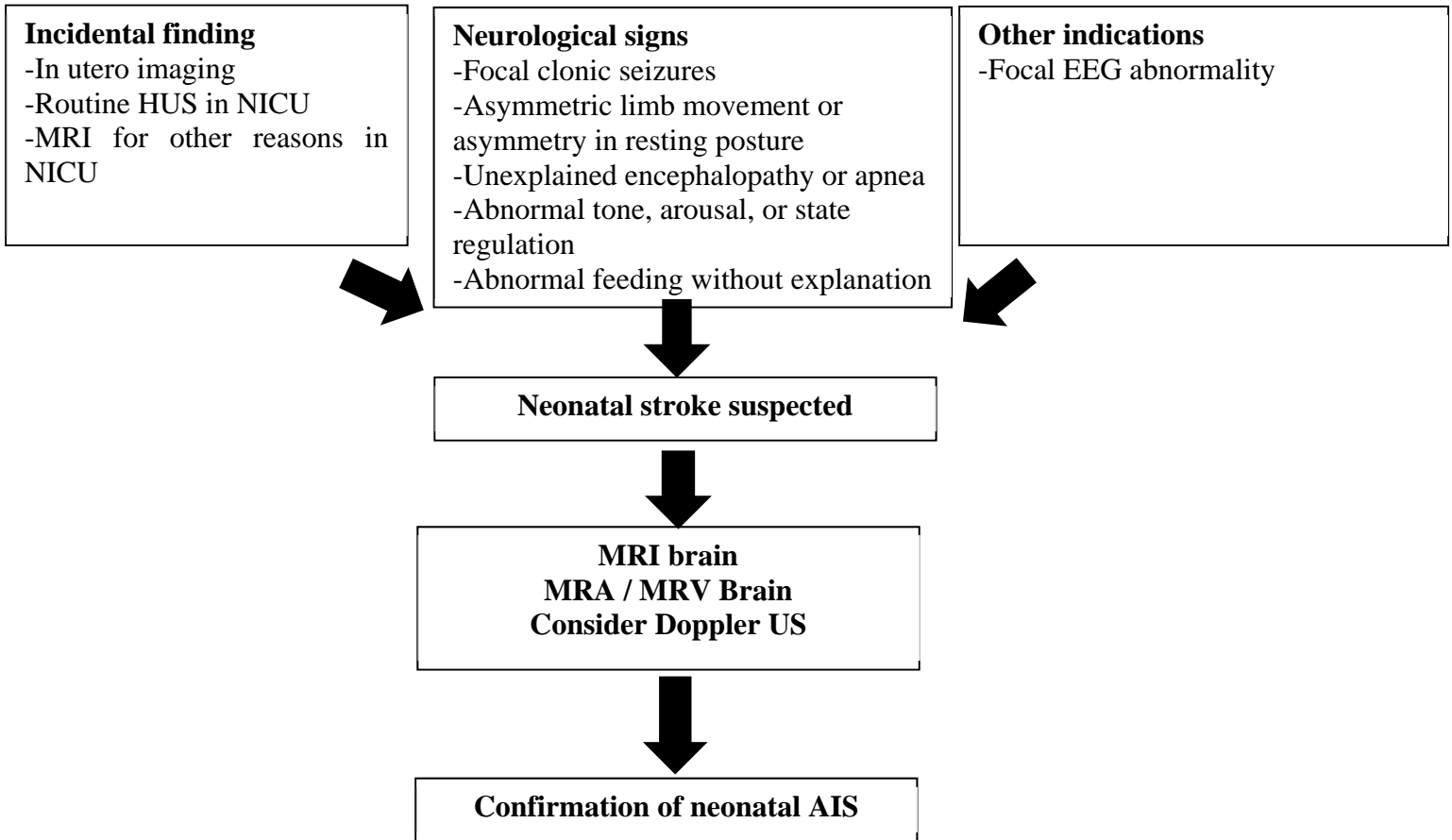
19. McQuillen PS, Barkovich AJ, Hamrick SE, et al. Temporal and anatomic risk profile of brain injury with neonatal repair of congenital heart defects. *Stroke*. 2007;38(2 Suppl):736-741.
20. McQuillen PS, Hamrick SE, Perez MJ, et al. Balloon atrial septostomy is associated with preoperative stroke in neonates with transposition of the great arteries. *Circulation*. 2006;113(2):280-285.
21. Martinez-Biarge M, Cheong JL, Diez-Sebastian J, Mercuri E, Dubowitz LM, Cowan FM. Risk Factors for Neonatal Arterial Ischemic Stroke: The Importance of the Intrapartum Period. *J Pediatr*. 2016;173:62-68 e61.
22. Lee J, Croen LA, Lindan C, et al. Predictors of outcome in perinatal arterial stroke: a population-based study. *Ann Neurol*. 2005;58(2):303-308.
23. Lee CC, Lin JJ, Lin KL, et al. Clinical Manifestations, Outcomes, and Etiologies of Perinatal Stroke in Taiwan: Comparisons between Ischemic, and Hemorrhagic Stroke Based on 10-year Experience in A Single Institute. *Pediatr Neonatol*. 2017;58(3):270-277.
24. Fox CK, Glass HC, Sidney S, Smith SE, Fullerton HJ. Neonatal seizures triple the risk of a remote seizure after perinatal ischemic stroke. *Neurology*. 2016;86(23):2179-2186.
25. Fox CK, Mackay MT, Dowling MM, et al. Prolonged or recurrent acute seizures after pediatric arterial ischemic stroke are associated with increasing epilepsy risk. *Dev Med Child Neurol*. 2017;59(1):38-44.
26. Harbert MJ, Tam EW, Glass HC, et al. Hypothermia is correlated with seizure absence in perinatal stroke. *J Child Neurol*. 2011;26(9):1126-1130.
27. Golomb MR, Garg BP, Edwards-Brown M, Williams LS. Very early arterial ischemic stroke in premature infants. *Pediatr Neurol*. 2008;38(5):329-334.
28. Govaert P, Smith L, Dudink J. Diagnostic management of neonatal stroke. *Semin Fetal Neonatal Med*. 2009;14(5):323-328.
29. Cowan F, Mercuri E, Groenendaal F, et al. Does cranial ultrasound imaging identify arterial cerebral infarction in term neonates? *Arch Dis Child Fetal Neonatal Ed*. 2005;90(3):F252-256.
30. Lee S, Mirsky DM, Beslow LA, et al. Pathways for Neuroimaging of Neonatal Stroke. *Pediatr Neurol*. 2017;69:37-48.
31. Siddiq I, Armstrong D, Surmava AM, et al. Utility of Neurovascular Imaging in Acute Neonatal Arterial Ischemic Stroke. *J Pediatr*. 2017;188:110-114.
32. Kirton A, deVeber G. Advances in perinatal ischemic stroke. *Pediatr Neurol*. 2009;40(3):205-214.
33. Roach ES, Golomb MR, Adams R, et al. Management of stroke in infants and children: a scientific statement from a Special Writing Group of the American Heart Association Stroke Council and the Council on Cardiovascular Disease in the Young. *Stroke*. 2008;39(9):2644-2691.
34. Monagle P, Chalmers E, Chan A, et al. Antithrombotic therapy in neonates and children: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest*. 2008;133(6 Suppl):887S-968S.



35. Cnossen MH, van Ommen CH, Appel IM. Etiology and treatment of perinatal stroke; a role for prothrombotic coagulation factors? *Semin Fetal Neonatal Med.* 2009;14(5):311-317.
36. Kurnik K, Kosch A, Strater R, et al. Recurrent thromboembolism in infants and children suffering from symptomatic neonatal arterial stroke: a prospective follow-up study. *Stroke.* 2003;34(12):2887-2892.
37. Golomb MR. Outcomes of perinatal arterial ischemic stroke and cerebral sinovenous thrombosis. *Semin Fetal Neonatal Med.* 2009;14(5):318-322.
38. Golomb MR, Saha C, Garg BP, Azzouz F, Williams LS. Association of cerebral palsy with other disabilities in children with perinatal arterial ischemic stroke. *Pediatr Neurol.* 2007;37(4):245-249.
39. Suppiej A, Mastrangelo M, Mastella L, et al. Pediatric epilepsy following neonatal seizures symptomatic of stroke. *Brain Dev.* 2016;38(1):27-31.
40. Westmacott R, Askalan R, MacGregor D, Anderson P, Deveber G. Cognitive outcome following unilateral arterial ischaemic stroke in childhood: effects of age at stroke and lesion location. *Dev Med Child Neurol.* 2010;52(4):386-393.
41. Chabrier S, Peyric E, Drutel L, et al. Multimodal Outcome at 7 Years of Age after Neonatal Arterial Ischemic Stroke. *J Pediatr.* 2016;172:156-161.e153.
42. Lehman LL, Rivkin MJ. Perinatal arterial ischemic stroke: presentation, risk factors, evaluation, and outcome. *Pediatr Neurol.* 2014;51(6):760-768.

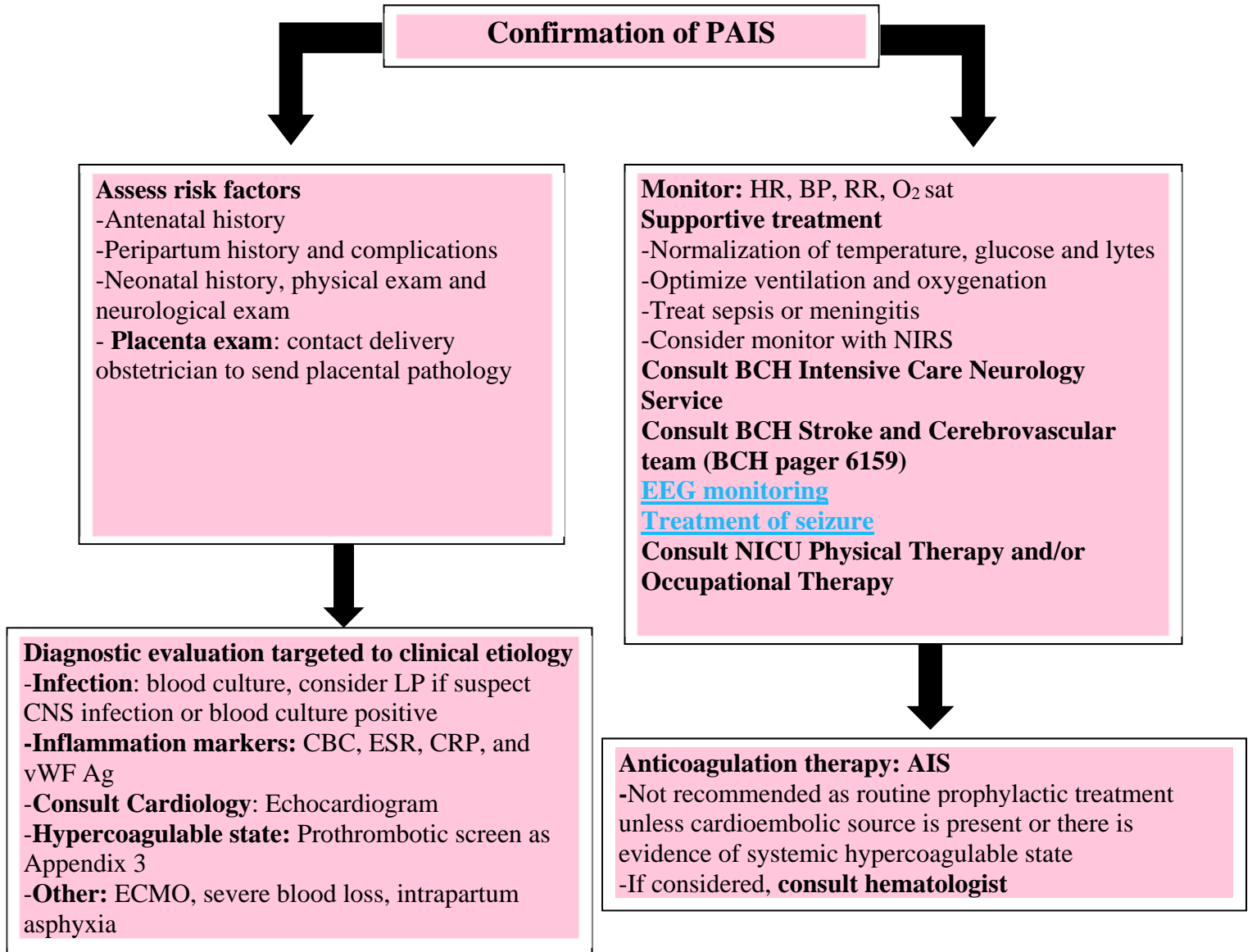


Appendix 1- Algorithm to identify of neonatal ischemic stroke





Appendix 2- Algorithm for evaluation and treatment of PAIS





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 thrombosis^{1,35,42})

B- Tests:

Plasma/Protein Based	DNA Based
Antiphospholipid antibodies Lupus anticoagulant* Anti-β2 glycoprotein 1 antibodies, IgG and IgM** Anti-cardiolipin antibodies, IgG, IgA and IgM** Protein C functional assay* Protein S* Plasminogen* Serum homocysteine level ^l Serum lipoprotein (a)** Fibrinogen* Factor VIIIc*	Factor V Leiden gene mutation* Prothrombin gene mutation* MTHFR mutation ^s

*Blue top Na citrate tube, 3 ml **Gold top tube, plain, gel, 4 ml, ^lLavender top tube, EDTA, 4 ml on ice (minimum 0.4 ml), ^sYellow 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:
 - 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
 - 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
 - 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:
 - 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.

Appendix 4 References:

1. Basu AP. Early intervention after perinatal stroke: opportunities and challenges. *Dev Med Child Neurol* 2014; 56:516.
2. Basu AP, Pearse JE, Baggaley J, Watson RM, Rapley T. Participatory design in the development of an early therapy intervention for perinatal stroke. *BMC Pediatrics*. 2017; 17: 33.
3. Guzetta A, Mercuri E, Rapisardi G, Ferrari F, Roversi MF, Cowan F, Rutherford M, Paolicelli PB, Einspieler C, Boldrini A, Dubowitz L, Prechtl HF, Cioni G. General movements detect early signs of hemiplegia in term infants with neonatal cerebral infarction. *Neuropediatrics*. 2003; 34: 61-66.
4. Hadders-Algra M. Early diagnosis and early intervention in cerebral palsy. *Front Neurol*. 2014 Sep 24;5:185.
5. Hamilton W, Huang H, Seiber E, Lo W. Cost and outcome in pediatric ischemic stroke. *J Child Neurol*. 2015; 30(11): 1483-1488.
6. Morgan C, Novak I, Badawi N. Enriched environments and motor outcomes in cerebral palsy: systematic review and meta-analysis. *Pediatrics*. 2013 Sep;132(3):e735-46.
7. Spittle A, Orton J, Anderson PJ, Boyd R, Doyle LW. Early developmental intervention programmes provided post hospital discharge to prevent motor and cognitive impairment in preterm infants. *Cochrane Database Syst Rev*. 2015 Nov 24;(11):CD005495.
8. Sreenan C, Bhargava R, Robertson CM. Cerebral infarction in the term newborn: clinical presentation and long-term outcome. *J Pediatr* 2000; 137:351.



BRIGHAM AND WOMEN'S HOSPITAL

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 stroke 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, occurring 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 electroencephalogram (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 at risk for motor deficits, subsequent seizures or developmental 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.



MRI



aEEG



cEEG

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