Gamil Fteeh, MD
Assistant Professor
Division of Pediatric Neurology
Department of Pediatrics
Loma Linda University School of Medicine
I have no relevant financial relationships to disclose
Objectives

1. To understand the pathophysiology and risk factors of stroke in children
2. To recognize symptoms and signs of acute stroke in children
3. To be familiar with the management options of stroke in children
4. To recognize the early complications of stroke in critical care setting and understand their management
Childhood Stroke

- Definition
- Epidemiology
- Pathophysiology
- Clinical Presentation
- Causes and risk factors
- Diagnostic evaluation
- Management
Definition
What is Stroke?

• Stroke is a disease that affects the arteries leading to and within the brain.

• It is the No. 5 cause of death and a leading cause of disability in the United States.

• A stroke occurs when a blood vessel that carries oxygen and nutrients to the brain is either blocked by a clot or bursts (or ruptures). When that happens, part of the brain cannot get the blood (and oxygen) it needs, so it and brain cells die.
What are the types of stroke?

Stroke can be caused either by

• A clot obstructing the flow of blood to the brain (called an ischemic stroke)

• Or by a blood vessel rupturing and preventing blood flow to the brain (called a hemorrhagic stroke).

• A TIA (transient ischemic attack), or "mini stroke", is caused by a temporary clot.
Epidemiology
Epidemiology

- The annual incidence rates of arterial ischemic stroke (AIS) in infants and children range from 0.6 to 7.9/100,000 children per year
  - Intracranial hemorrhage 1-2
  - Cerebral sinovenous thrombosis 0.7
Canadian Pediatric Ischemic Stroke Registry: Arterial Ischemic Stroke—Epidemiology

N=933 Children with AIS


Pathophysiology of Stroke
3 years old female was admitted to PICU after cardiac arrest due to drowning, status post CPR. Her MRI brain showed stroke in the following regions.
3 years old female was admitted to PICU after cardiac arrest due to drowning, status post CPR. The mechanism of her stroke is mostly

1. Thrombus (blood clot) develops at the clogged part of the vessel
2. Embolism: blood clot that forms at another location in the circulatory system, usually the heart and large arteries of the upper chest and neck.
3. Hypoperfusion (watershed stroke)
4. Hypoxic ischemic injury
Stroke mechanism

Thrombosis

- Thrombus (blood clot) develops at the clogged part of the vessel.
  - disease of the arterial wall, such as aretiopathy or dissection
  - There may or may not be superimposed thrombosis
Embolism

- A blood clot that forms at another location in the circulatory system, usually the heart and large arteries of the upper chest and neck.
Stroke mechanism

Hypoperfusion (watershed stroke)
- Post cardiac arrest
- Arteriopathy
Pathophysiology of Stroke
Pathophysiology of Stroke

- Ischemic penumbra

- Infarcted tissue
  - Penumbra
    - Metabolic failure (Ion pumps)
    - Electrophysiologic failure (Isoelectric EEG)
  - Normal tissue

- CBF: mL·100 g⁻¹·min⁻¹
  - 15
  - 30
  - 50
Pathophysiology of Stroke

Decreased CBF

deprivation of O2 and glucose in brain tissue
The Ischemic Penumbra

- Potentially reversible electrophysiologic failure due to energy deprivation but have not had the cascade leading to neuronal death

- It is the target of neuroprotective treatment in ischemic stroke
Pathophysiology of Stroke

CT perfusion

- The three parameters typically used in determining the two areas:
  - Core infarct
  - Penumbra

1. Time to peak of the deconvolved tissue residue function (Tmax)

2. Cerebral blood flow (CBF)

3. Cerebral blood volume (CBV)
Clinical Presentation
6 year old male is admitted to PICU with heart failure due to dilated cardiac myopathy, 2 days later, you noticed new neurological symptoms that make you highly concern for stroke. All the following neurological findings are highly suggesting for stroke except one:

1. Lower extremities weakness
2. Aphasia
3. Slurred speech
4. Left arm and leg weakness
5. Weakness of lower side of right face (facial droop)
Clinical Presentation in childhood Stroke

- Focal neurologic deficits
  - Hemiparesis
  - Aphasia, ataxia, dysarthria, visual deficits, and cranial nerve palsies

- Seizures

- Headache
  - A sudden-onset thunderclap headache or neck, shoulder, or occipital pain “cervical artery dissection”
Clinical Presentation in childhood Stroke

- Stuttering/fluctuating course of neurologic deficits “vasculopathy”

- Recurrent TIAs “vasculopathy” or “thromboembolic source”.

- History of paroxysmal episodes of focal neurologic dysfunction precipitated by hyperventilation “Moyamoya”
CNS Arterial Circulation

Anterior Circulation
- from Internal Carotid

Posterior Circulation
- Vertebral-Basilar
CNS Arterial Circulation
ANTERIOR CIRCULATION

Internal Carotid, Middle & Anterior Cerebral Arteries):

- Unilateral motor &/or sensory deficit: face=arm>leg.

- Cortical deficit:
  - visual field cut
  - gaze preference
  - aphasia if dominant hemisphere
  - extinction/neglect if non-dominant hemisphere.
**Posterior CIRCULATION**

**Cerebellar:**
- ataxic gait, dysmetria, dysarthria

**Unilateral brainstem deficits:**
- Pure motor hemiparesis
- Oculomotor defects
- Double vision
- Vertigo
- Tongue deviation
- Dysarthria/dysphagia

**Occipital cortex:**
- visual field loss
Causes and Risk Factors
Causes and Risk Factors

Coagulation → Vasculature

Heart & Aorta
Causes and Risk Factors

Coagulation

Vasculature

Heart & Aorta

Arteriopathies:
- Genetic/syndromic (e.g. NF, alagille)
- Traumatic (dissection)
- Degenerative (post XRT)
- Inflammatory (infectious, autoimmune)
- Compressive (tumors)
- Sickle cell vasculopathy
- Iatrogenic
- Unknown (e.g. moyamoya)
Causes and Risk Factors

Coagulation

Vasculature

Heart & Aorta

Cardiac-Aortic Embolism

- “Trans-cardiac” – right-to-left shunts w PFO, CHD
- Intracardiac clots – myocarditis, cardiomyopathy, arrhythmias, valve disease, heart failure
- Peri-procedural – heart surgery, catheterization
- Device-related – VAD, ECMO, artificial valves
- Intracardiac tumors
Causes and Risk Factors

**Procoagulant conditions**
- Genetic thrombophilias (factor deficiencies, folate defects, mutations in fibrinolytic pathways)
- Autoimmune thrombophilias (APLAS)
- Hematologic disorders (Hgb SS, anemia)
- Drugs (IV Ig, aspariginase)
- Protein-losing conditions (enteropathies, nephropathies, liver failure)
A total of 676 children were included

- Arteriopathies (53%)
- Cardiac disorders (31%)
- Infection (24%)
- Acute head and neck disorders (23%)
- Acute systemic conditions (22%)
- Chronic systemic conditions (19%)
- Prothrombotic states (13%)
- Chronic head and neck disorders (10%)
- Atherosclerosis-related RFs (2%)
- Others (22%)
- No identifiable RFs 54 (9%)
# Arterial Ischemic Stroke Risk Factors: The International Pediatric Stroke Study

Mark T. Mackay, MBBS, Max Wiznitzer, MD, Susan L. Benedict, MD, Katherine J. Lee, MSc, PhD, Gabrielle A. deVeber, MSc, MD, and Vijeya Ganesan, MD, on behalf of the International Pediatric Stroke Study Group

## Arteriopathies (53%)

<table>
<thead>
<tr>
<th>Arteriopathy</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Focal cerebral arteriopathy</td>
<td>69</td>
</tr>
<tr>
<td>Moyamoya</td>
<td>61</td>
</tr>
<tr>
<td>Arterial dissection</td>
<td>56</td>
</tr>
<tr>
<td>Vasculitis</td>
<td>33</td>
</tr>
<tr>
<td>Sickle cell arteriopathy</td>
<td>21</td>
</tr>
<tr>
<td>Post varicella arteriopathy</td>
<td>19</td>
</tr>
<tr>
<td>Other</td>
<td>10</td>
</tr>
<tr>
<td>Unspecified arteriopathy</td>
<td>9</td>
</tr>
</tbody>
</table>

Total: 277/525 (53%)

## Cardiac disorders (CDs) (31%)

<table>
<thead>
<tr>
<th>Cardiac disorder</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congenital heart disease</td>
<td>121</td>
</tr>
<tr>
<td>Acquired heart disease</td>
<td>40</td>
</tr>
<tr>
<td>Isolated PFO</td>
<td>31</td>
</tr>
<tr>
<td>&lt;72 hours after cardiac surgery</td>
<td>32</td>
</tr>
<tr>
<td>Previous cardiac surgery</td>
<td>33</td>
</tr>
<tr>
<td>Cardiac catheterization</td>
<td>17</td>
</tr>
<tr>
<td>ECMO</td>
<td>11</td>
</tr>
</tbody>
</table>

Total: 204/667 (31%)
# Arterial Ischemic Stroke Risk Factors: The International Pediatric Stroke Study

Mark T. Mackay, MBBS, Max Wiznitzer, MD, Susan L. Benedict, MD, Katherine J. Lee, MSc, PhD, Gabrielle A. deVeber, MSc, MD, and Vijaya Ganesan, MD, on behalf of the International Pediatric Stroke Study Group

## Prevalence of Risk Factors by Age at Time of AIS

<table>
<thead>
<tr>
<th>Risk Factor Category</th>
<th>&lt;5 Years</th>
<th>5–9 Years</th>
<th>10–14 Years</th>
<th>15–18 Years</th>
<th>$p^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arteriopathy</td>
<td>106/229 (46%)</td>
<td>82/125 (66%)</td>
<td>57/106 (54%)</td>
<td>32/65 (49%)</td>
<td>0.006</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>115/317 (36%)</td>
<td>39/141 (28%)</td>
<td>26/129 (20%)</td>
<td>24/80 (30%)</td>
<td>0.007</td>
</tr>
<tr>
<td>Chronic systemic conditions</td>
<td>49/321 (15%)</td>
<td>34/144 (24%)</td>
<td>26/129 (20%)</td>
<td>17/80 (21%)</td>
<td>0.15</td>
</tr>
<tr>
<td>Prothrombotic states</td>
<td>36/321 (11%)</td>
<td>16/144 (11%)</td>
<td>23/129 (18%)</td>
<td>12/80 (15%)</td>
<td>0.23</td>
</tr>
<tr>
<td>Acute systemic conditions</td>
<td>94/308 (31%)</td>
<td>25/142 (18%)</td>
<td>22/129 (17%)</td>
<td>7/79 (9%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Chronic head and neck disorders</td>
<td>10/318 (3%)</td>
<td>17/142 (12%)</td>
<td>28/128 (22%)</td>
<td>12/79 (15%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Acute head and neck disorders</td>
<td>81/306 (26%)</td>
<td>33/139 (24%)</td>
<td>19/124 (15%)</td>
<td>15/79 (19%)</td>
<td>0.07</td>
</tr>
<tr>
<td>Infection</td>
<td>72/321 (22%)</td>
<td>23/144 (16%)</td>
<td>24/130 (18%)</td>
<td>8/81 (10%)</td>
<td>0.05</td>
</tr>
<tr>
<td>At least 1 RF present</td>
<td>191/214 (89%)</td>
<td>110/118 (93%)</td>
<td>81/98 (83%)</td>
<td>59/63 (94%)</td>
<td>0.05</td>
</tr>
</tbody>
</table>
Childhood Stroke: Laboratory Studies

FOR ED:
- **CARDIAC**: EKG
- **BASIC LABS**: basic metabolic panel, CBC, Plts, PT, PTT
- **INFECTION**: If acute febrile illness consider LP

FOR IN-PT w/u:
- **ECHOCARDIOGRAM**
- **THROMBOPHILIA**
- **METABOLIC**:
  - consider if stroke not in classic vascular distribution, (CSF lactate, plasma lactate/pyruvate, plasma amino acids, urine organic acids.)
- **RHEUMATOLOGIC DISEASE**:
  - consider this if systemic autoimmune signs, multifocal/small vessel distribution, (“inflammogram” lab markers, consult Rheumatology service & consider catheter angiogram).
Diagnostic Evaluation: Imaging

- CT: rapid screen to rule out hemorrhage, insensitive in early AIS, fairly sensitive to screen for CSVT

- MRI with DWI (ADC map): essential for sensitive & specific differentiation of stroke from other diagnoses.

- Vascular imaging:
  - MRA brain - good (not perfect) sensitivity & specificity
  - MRA neck – necessary for all cryptogenic AIS
  - Obtain early to aid decision-making regarding antithrombotic rx
  - MRV for suspected CSVT
  - CT Angiogram – for vascular imaging if cannot get MRI
  - Conventional angiography
Acute Stroke Neuroimaging: CT insensitive

- 9 year old female with sudden onset right sided weakness (face arm leg), inability to look to right, slurred speech and fluctuating level of consciousness

Negative Head CT
~ 1 hour after onset

MRI DWI ~ 5 hours after symptom onset

Corresponding ADC map
Pediatric Ischemic Stroke Management
• 10 years old right handed girl with history of migraine, presented from trampoline game with one hour history of left arm and leg weakness and slurred speech, on exam she is alert, awake, her speech is slurred, no aphasia, has left facial droop, left arm/leg weakness. Her MRI showed ischemic stroke in right middle cerebral artery territory. She is admitted to PICU. All the following regarding ICU management are wrong except for:

1. Head of bed elevated 30 degree.
2. Hypothermia to 34-36 C will improve her neurological outcome.
3. Her IV fluids should not have dextrose
4. Target systolic blood pressure (SBP) 10-90%ile for age to maintain cerebral perfusion pressure.
5. Anti-seizure medication is recommended for prophylaxis.
Her MRA head and neck showed right ICA dissection, she was placed on Heparin drip, 24 hours later she developed alerted mental status, what is the best next step in evaluation:

1. Check PTT
2. Check glucose
3. LP
4. CT head without contrast
5. EEG
CT head showed severe edema in right MCA territory with 4 mm left midline shift, what is the best management to reduce mortality

1. HOB elevated 30 degree
2. Decompressive hemicraniectomy
3. Keep Na 145-155
4. Mannitol
5. Hypertonic saline
Pediatric Ischemic Stroke Management

• Is it stroke or not?

• Past medical History
  ▫ Cardiac, malignancy, SCD, genetic, metabolic, inflammatory, autoimmune diseases

• Previously healthy- trauma? Drugs?

• What is the possible pathophysiology?
Pediatric Ischemic Stroke Management

- No randomized controlled trials

- Largely adapted from treatment of adult stroke

- Clinical experience of experts
Pediatric Ischemic Stroke Management

1. Hyperacute Treatment
   - Neuroprotective care
   - Thrombolysis and Endovascular Therapy
   - Initial antithrombotic treatment
     - Antiplatelet (aspirin, clopidogrel)
     - Anticoagulant (heparins, warfarin)

2. Secondary prevention

3. Search for etiology and risk factors during the initial phase
   - Acute treatment for specific causes
Pediatric Ischemic Stroke Management

1. Hyperacute Treatment
   - Neuroprotective care
   - Thrombolysis and Endovascular Therapy
   - Initial antithrombotic treatment
     • Antiplatelet (aspirin, clopidogrel)
     • Anticoagulant (heparins, warfarin)

2. Secondary prevention

3. Search for etiology and risk factors during the initial phase
   - Acute treatment for specific causes
Pediatric Ischemic Stroke Management

**PICU Rule**

- Neuroprotective care
- Recognize early stroke
- Recognize recurrent stroke
  - Higher risk within first few days of stroke
- Recognize complications of stroke or stroke treatment
  - Hemorrhagic conversion
  - Malignant cerebral edema
Neuroprotective care
Neuroprotective care

Goals:

- Prevent recruitment of the ischemic penumbra
- The prevention of secondary injury
  - caused by pathological changes in blood pressure, oxygenation, and temperature or impaired glucose regulation
Neuroprotective care

- Keep the head of the patient’s bed flat
- **Normal O2**: Titrate O2 to maintain SPO2 > 92%
- **Normovolemia**: Isotonic fluid (i.e., 0.9% NaCl) at maintenance
- **Normoglycemia**
- **Normotension**
- **Normothermia**
- **Seizure control**
Neuroprotective care

**Glucose**

- Adult Guidelines *(Stroke. 2013;44:870-947)*
  - Hyperglycemia during the first 24 hours after stroke is associated with worse outcomes than normoglycemia.
  - 140 to 180 mg
Neuroprotective care

Temperature:

- Patients with stroke and other brain injuries, fever is consistently associated with worse outcomes across multiple outcome measures.

Impact of Fever on Outcome in Patients With Stroke and Neurologic Injury

A Comprehensive Meta-Analysis

David M. Greer, MD, MA; Susan E. Funk, MBA; Nancy L. Reaven, MA;
Myrsini Ouzounelli, MD; Gwen C. Uman, RN, PhD

(Stroke. 2008;39:3029-3035)
Neuroprotective care

**Temperature:**

- Hypermetabolic state
- Increase metabolic demand
- Impaired substrate delivery as in ischemia

Supply-demand imbalance, and further neuronal injury
Neuroprotective care

Autoregulation
Neuroprotective care

Impaired Autoregulation

Graph showing cerebral blood flow vs. mean arterial pressure (mmHg). The graph compares normal (blue line) and acute stroke (red line) conditions. The optimal brain CBF is indicated by a green shaded area between the two lines.
# Neuroprotective Care

## Blood Pressure:

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Risk Ratio</th>
<th>95% CI</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>12-mo mortality</td>
<td>4.5</td>
<td>0.6-34.6</td>
<td>0.096</td>
</tr>
<tr>
<td>Death during hospital admission</td>
<td>1.7</td>
<td>1.4-2.0</td>
<td>0.52</td>
</tr>
<tr>
<td>Recurrent stroke</td>
<td>1.3</td>
<td>0.48-3.3</td>
<td>0.64</td>
</tr>
<tr>
<td>Any neurologic deficit</td>
<td>1.1</td>
<td>0.83-1.3</td>
<td>0.66</td>
</tr>
</tbody>
</table>

**Table 5** Relationship between acute poststroke hypertension and 12-month outcome

---

**Hypertension at time of diagnosis and long-term outcome after childhood ischemic stroke**

Lauren N. Brush, MBBS  
Paul T. Monagle, MD  
Mark T. Mackay, MBBS  
Anne L. Gordon, PhD

**Conclusions:** HPT is prevalent in children with IS in the first 3 days after diagnosis and is associated with increased risk of death. Larger prospective studies involving systematic recording of blood pressure are required to delineate the impact of HPT on risk of death or disability. *Neurology* 2013;80:1225-1230
Neuroprotective care

**Blood Pressure:**

Current Practice

- Recommend a blood pressure goal of the 50th-90th percentile for age and height
Neuroprotective care

**Seizures:**

Increase metabolic demand
Neuroprotective care

Seizures:

Increase metabolic demand

Compromise ischemic penumbra
Neuroprotective care

**Seizures:**

- Increase metabolic demand
- Compromise ischemic penumbra
- Progression of an infarct
Neuroprotective care

Seizures:

• Childhood Guidelines
  (Stroke 2008;39:2644-2691)

  ▫ In the absence of clinical or electrographic seizures, prophylactic administration of antiepileptic medications in children with ischemic stroke is not necessary (Class III, Level of Evidence C).
Neuroprotective care

- Keep the head of the patient’s bed flat
- **Normal O2**: Titrate O2 to maintain SPO2 > 92%
- **Normovolemic**: Isotonic fluid (i.e., 0.9% NaCl) at maintenance
- **Normoglycemia**: For age >2, no glucose in IV fluids unless hypoglycemic
- **Normotension**: Target systolic blood pressure (SBP) 50-90%ile for age to maintain cerebral perfusion pressure.
- **Normothermia**: Treat all T > 37°C with acetaminophen
- **Seizure control**: Administer anti-seizure medication ASAP with any suspected seizure activity
Management of Stroke Complications

Hemorrhagic transformation

• 30% of children with acute arterial stroke

• Was associated with larger infarct volumes

• Usually petechial and asymptomatic (only 3% symptomatic)

• Less common in children with vasculopathy

• Not significantly associated with anticoagulation versus antiplatelet therapy (relative risk, 0.6; 95% CI, 0.2 to 1.5; P 0.26)

(Stroke 2011;42:941-946.)
Management of Stroke Complications

(Stroke. 2011;42:941-946.)
Management of Stroke Complications

Malignant cerebral edema

- Large-vessel ischemic stroke or significant hemorrhagic transformation

- Early neurosurgical consultation
  - decompressive hemicraniectomy
Management of Stroke Complications

Malignant cerebral edema

- In adults, decompressive hemicraniectomy performed within 48 hours of stroke onset significantly reduced mortality in patients under age 60 years.

- The use of decompressive hemicraniectomy in children with malignant cerebral edema can be life-saving and has been associated with moderately good functional outcomes.

- Medical management, including intracranial pressure monitoring, might not be beneficial and may result in delayed surgery.
Management of Stroke Complications
3 years old female was admitted to PICU after cardiac arrest due to drowning, status post CPR. Her MRI brain showed stroke in the following regions
3 years old female was admitted to PICU after cardiac arrest due to drowning, status post CPR. The mechanism of her stroke is mostly

1. Thrombus (blood clot) develops at the clogged part of the vessel
2. Embolism: blood clot that forms at another location in the circulatory system, usually the heart and large arteries of the upper chest and neck.
3. Hypoperfusion (watershed stroke)
4. Hypoxic ischemic injury
6 year old male is admitted to PICU with heart failure due to dilated cardiac myopathy, 2 days later, you noticed new neurological symptoms that make you highly concern for stroke. All the following neurological findings are highly suggesting for stroke except one:

1. Lower extremities weakness
2. Aphasia
3. Slurred speech
4. Left arm and leg weakness
5. Weakness of lower side of right face (facial droop)
- 10 years old right handed girl with history of migraine, presented from trampoline game with one hour history of left arm and leg weakness and slurred speech, on exam she is alert, awake, her speech is slurred, no aphasia, has left facial droop, left arm/leg weakness. Her MRI showed ischemic stroke in right middle cerebral artery territory. She is admitted to PICU. All the following regarding ICU management are wrong except for:

1. Head of bed elevated 30 degree.
2. Hypothermia to 34-36 C will improve her neurological outcome.
3. Her IV fluids should not have dextrose
4. Target systolic blood pressure (SBP) 10-90%ile for age to maintain cerebral perfusion pressure.
5. Anti-seizure medication is recommended for prophylaxis
Her MRA head and neck showed right ICA dissection, she was placed on Heparin drip, 24 hours later she developed alerted mental status, what is the best next step in evaluation:

1. Check PTT
2. Check glucose
3. LP
4. CT head without contrast
5. EEG
CT head showed severe edema in right MCA territory with 4 mm left midline shift, what is the best management to reduce mortality

1. HOB elevated 30 degree
2. Decompressive hemicraniectomy
3. Keep Na 145-155
4. Mannitol
5. Hypertonic saline
Management: A Team Approach

**Symptom Onset**
- Community awareness, field triage, early referral
- Transport, Emerg Med, Nursing
  - Recognition & Initial Rx
- Neuro, NroRad, ICU, Heme, Cardiol, Nsg, IR
  - Complete Dx, Stroke-Specific Rx

**Stroke Team:**
- Neuro Fellow, Attnd Neuro, RN, SW
- PM&R, SW, Neuro, Heme
- PM&R, SW, Neuropsych, Neuro, Heme

**Recovery**
- In-Pt Rehab, 2° Prevention
- Out-Pt Rehab, Back To Home, School
- Back To Home, School
Summary

• Stroke is a disease that affects the arteries leading to and within the brain.

• Stroke mechanism: thrombotic, embolic, hypoperfusion

• Neuroprotective care is the core management of stroke in PICU

• Ischemic Penumbra is the target of neuroprotective treatment in stroke
Childhood Stroke

Team work
( ED, PICU, Neurosurgery, Neuroradiology, Hematology, PM&R, Neurology)
Thank You