UPDATE ON THE MANAGEMENT OF NEONATAL THROMBOSIS

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Disclosure

• The following relationships with commercial interests related to this presentation existed during the past 12 months:
  – Nothing to disclose

• The following FDA disclosures related to this presentation exist:
  – Unfractionated heparin (UFH) - off-label use
  – Low molecular weight heparin (LWMH) - off-label use
  – Recombinant Tissue Plasminogen Activator (rTPA) - off-label use
  – Nitroglycerin ointment – off-label use
  – Antithrombin 3 concentrate- off-label use

*In other words, everything I recommend*
Case Presentation

• Baby A is 3-day old, 39-week infant born by urgent cesarean section
  – Failure to progress, prolonged rupture of membranes, and chorioamnionitis
  – G1 mother with no other prenatal abnormalities

• Developed tachypnea after birth and placed on nasal cannula

• Ampicillin and Gentamicin started but stopped at 48-hours due to negative blood cultures
Case Presentation

- Currently on room air and taking full PO breast milk feedings
- On exam, palpable mass in the RLQ
- Last 3 diapers have been dry
- History of admission platelet count of 95 x 10^3/L
  - Heel stick specimen
  - CBC ordered for following morning
Case Presentation

- Stat creatinine obtained and value 1.9 mg/dL
- Renal US demonstrates bilateral renal vein thromboses with extension into the IVC
  - Adrenal hemorrhage also observed

Dilemma

- Faced with acute renal failure with bilateral renal vein thromboses and an adrenal hemorrhage.
- Not sure what to do as there are no evidence-based protocols.
Objectives

- Briefly review neonatal hemostatic system
- Types of neonatal thromboses
- Perinatal and prothrombotic risk factors
- Evaluation and management protocols
Important Points

• Thrombosis is a significant problem affecting both term and preterm infants
• Most neonates that develop thrombosis have predisposing disorders and triggers
• Sepsis is a powerful promoter of prothrombotic hemostatic alterations
• Genetic thrombophilia contributes to thrombotic tendency of newborn
“Recommendations for neonatal treatment are based on extrapolation of principles of therapy from adult guidelines, limited clinical information from registries, individual case studies, and knowledge of current common clinical practice.”

Introduction

- Newborns have the greatest risk for thromboembolism (TE)
- Venous TE is slightly more frequent than arterial
- Equal gender distribution

<table>
<thead>
<tr>
<th>Registry</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>German</td>
<td>5.1/100,000 births</td>
</tr>
<tr>
<td>(symptomatic events)</td>
<td></td>
</tr>
<tr>
<td>Canadian</td>
<td>2.4/1000 admissions</td>
</tr>
<tr>
<td>(excluded stroke)</td>
<td></td>
</tr>
</tbody>
</table>
The Neonatal Coagulation System

Cell-Based Coagulation Model*

Initiation

Platelet

Amplification

Propagation

## Coagulation Protein Levels in Neonates

<table>
<thead>
<tr>
<th>Increased (Compared with adults)</th>
<th>Decreased (Compared with adults)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factor VIII</td>
<td>Factor II</td>
</tr>
<tr>
<td></td>
<td>Factor VII</td>
</tr>
<tr>
<td></td>
<td>Factor IX</td>
</tr>
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<td></td>
<td>Factor X</td>
</tr>
<tr>
<td></td>
<td>Factor XI</td>
</tr>
<tr>
<td></td>
<td>Factor XII</td>
</tr>
</tbody>
</table>

# Anticoagulant Levels in Neonates

<table>
<thead>
<tr>
<th>Anticoagulant</th>
<th>Term  (Day 5)</th>
<th>Preterm (Day 5)</th>
<th>Adult</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antithrombin  (U/ml)</td>
<td>0.67 (0.41-0.93)</td>
<td>0.56 (0.4-0.82)</td>
<td>1.05 (0.79-1.31)</td>
</tr>
<tr>
<td>Protein C  (U/ml)</td>
<td>0.42 (0.2-0.64)</td>
<td>0.31 (0.11-0.51)</td>
<td>0.96 (0.64-1.28)</td>
</tr>
<tr>
<td>Protein S  (U/ml)</td>
<td>0.5 (0.22-0.78)</td>
<td>0.37 (0.13-0.61)</td>
<td>0.92 (0.6-1.24)</td>
</tr>
<tr>
<td>Plasminogen  (U/ml)</td>
<td>2.17 (1.41-2.93)</td>
<td>1.91 (1.21-2.61)</td>
<td>3.36 (2.48-4.24)</td>
</tr>
</tbody>
</table>

Neonatal Coagulation System

At Birth

Hemorrhage

Thrombosis
Conceptualization of Risk Factors for Neonatal Thrombosis

Maternal Factors:
- Infertility
- Oligohydramnios
- Thrombotic states
- Preeclampsia
- Autoimmunity
- Diabetes
- Chorioamnionitis

Fetal/Neonatal Factors:
- Catheters
- CHD
- Infection
- RDS
- Dehydration
- Birth Asphyxia
- Polycythemia
- Inherited thrombophilias

Neonatal Thrombosis
Types of Neonatal Thromboses
## Type of Neonatal Thromboses

<table>
<thead>
<tr>
<th>Arterial</th>
<th>Venous</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ischemic perinatal stroke</strong></td>
<td><strong>Catheter related thrombosis</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Right atrial and SVC thrombi</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Renal vein thrombosis</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Cerebral sinovenous thrombosis (CSVT)</strong></td>
</tr>
<tr>
<td>Iatrogenic or spontaneous thrombosis in aorta, iliac, and femoral arteries</td>
<td></td>
</tr>
</tbody>
</table>
Arterial Ischemic Stroke

• 1 per 2300-5000 live births*

• Signs and symptoms
  – Seizures, altered consciousness, tone abnormalities, feeding difficulties

• Typical distribution in term neonates is left middle cerebral artery**


Iatrogenic/Spontaneous Arterial Thrombosis

• Predisposition
  – Small caliber of vessel, vascular damage during insertion, location of catheter, composition of materials infused through catheter

• Types of catheters
  – Femoral artery catheter
    • Highest incidence of thrombosis
  – UAC*
    • Symptomatic thromboses is rare (1-3%) but mortality and morbidity of complication is high
    • Probability of developing aortic thrombus with UAC increases proportionally to duration of placement
      – 16% in 1 day; 32% in 7 days; 56% in 14-days; 80% in 21-days

Central Venous Catheter Related Thrombosis

• Signs and symptoms
  – Persistent infection/blood cultures
  – Thrombocytopenia
  – Line dysfunction
  – Swollen extremity
  – Chylothorax
Infection, Inflammation, and Thrombosis*

- Reciprocal relationship between catheter-related blood stream infection and thrombosis
- Fibrin sheaths formed around catheter tip serve as nidus for bacterial growth
- Inflammation from infection activates coagulation promoting thrombin formation on indwelling catheters

Central Venous Catheter Related Thrombosis

• UVC*
  – High rate of transient, asymptomatic thrombosis
  – Hematocrit > 55% risk factor in preterm infants
  – Portal venous thrombosis due to improper placement/omphalitis

• PICC lines*
  – Use of 0.5 U/kg/hour of UFH prolongs patency but does not reduce risk for thrombosis or infection

Renal Vein Thrombosis

- Most common site of spontaneous thrombosis in newborn
- 25% bilateral
  - 52-60% extend into the IVC
- Presentation
  - Hematuria, palpable flank mass, thrombocytopenia
- Outcomes
  - 70% of affected kidneys irreversible atrophy
  - 20% hypertension; 3% chronic renal failure

Cerebral Sinovenous Thrombosis*

- **Presentation**
  - Seizures, lethargy

- **Pathophysiology**
  - Hemorrhagic venous infarctions > 50%
  - Term infant with IVH (31%)
  - Thalamic hemorrhages

- **Outcomes**
  - 8-19% mortality rate
  - 23-54% with long-term neurologic complications
  - Recanalization in 75% of cases by 1-year

Purpura Fulminans

• Acute, lethal syndrome of DIC characterized by rapidly progressive hemorrhagic necrosis of the skin due to dermal vascular thrombosis

• Causes
  – Homozygous protein C deficiency (most common)
  – Homozygous protein S deficiency
  – Compound heterozygous states
  – Sepsis

# Recommended Imaging Modalities for Neonatal Thrombosis

<table>
<thead>
<tr>
<th>Vessel</th>
<th>Type/Location</th>
<th>Modality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial</td>
<td>Ischemic perinatal stroke</td>
<td>Diffusion weighted MRI / MRA</td>
</tr>
<tr>
<td></td>
<td>Iatrogenic or spontaneous</td>
<td></td>
</tr>
<tr>
<td>Venous</td>
<td>IVC, abdominal veins, lower extremities</td>
<td>Doppler Ultrasound</td>
</tr>
<tr>
<td></td>
<td>Renal Vein</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Portal Venous</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cerebral Sinovenous</td>
<td>Diffusion Weighted MRI w/ venography</td>
</tr>
<tr>
<td></td>
<td>Right Atrium and SVC</td>
<td>Echocardiography</td>
</tr>
</tbody>
</table>
Genetic Thrombophilia

• Genetic mutations resulting in prothrombotic phenotype
• Supporting evidence that genetic thrombophilia is a risk factor for neonatal thrombosis and stroke (especially idiopathic)
  – Role in pathogenesis of neonatal thrombosis is controversial and not completely understood
• Conflicting data in neonates with catheter-related thrombosis
Inheritance of Multiple Congenital Prothrombotic Risk Factors

• Risks of recurrent thromboses are increased with combined inherited defects*
  – Recurrent thromboses
    • OR 4.6 (95% CI 2.3 - 9.0) with single gene defect
    • OR 24.0 (95% CI 5.3 - 108.7) for combined defect

Inherited Thrombophilia

Environmental or Clinical Risk Factors
Inherited Pro-thrombotic Risk Factors

- Factor V Leiden deficiency*
- Factor II G20210A gene mutation
- Increased Apolipoprotein (a)
- Methylene-tetrahydrofolate reductase gene mutation (MTHFR C677T) genotype*
- Protein C-deficiency
- Protein S-deficiency
- Antithrombin-deficiency*
- Heparin cofactor II-deficiency
- Dysfibrinogenemia
- Plasminogenemia
- Hyperhomocysteinemia
- Increased levels of factor VIII, IX, XI, or fibrinogen
- Antiphospholipid antibody
- Anticardiolipin antibody
- Lupus anticoagulant
- Chromosome 2q13 deletion

*Increased risk for arterial thrombosis
Evaluation For Genetic Thrombophilia

• Age-appropriate reference ranges have been established for platelet counts, coagulation screening tests, and coagulation and anticoagulation proteins in preterm and term neonates*

Evaluation For Genetic Thrombophilia

• A step-wise approach based on pre/ante/postnatal risk factors

• ± Initial prothrombotic evaluation done in NICU
  – Depending on type/severity of thrombosis

• Blood samples sent to proper laboratory

• Follow-up diagnostic evaluation with Pediatric Hematology at 3-6 months
Important Reminders Concerning Thrombophilia Evaluation

• Protein based assays (if initially done) must be repeated within 3-6 months
  – May do initial evaluation at 3-6 months
  – Lower levels in newborn period make diagnosis of mild deficiency difficult

• DNA assays are reliable when done
  – Do not need to repeat

• If anticoagulation is being administered, obtain levels 14-30 days after discontinuing medication
Complete Laboratory Evaluation*

- Complete blood count
- PT, PTT
- Fibrinogen
- Antiphospholipid antibody panel
- Protein C and S activity levels
- Antithrombin activity assay
- Factor V G1691A (Leiden mutation)***
- Prothrombin G 20210A***
- MTHFR***
- Homocysteine level
- Lipoprotein (a)

- Factor VIII Activity
- Factor IX Activity
- Factor XI Activity
- Factor XII Activity
- Plasminogen activity
- Heparin cofactor II


**Blood Center of Wisconsin

***DNA-based assays
THE BEST VAMPIRE EVER

Take that Edward Cullen
Initial Neonatal Evaluation for Treatment/Thrombophilia Evaluation
Done in NICU

- Complete blood count
- PT, PTT
- Fibrinogen
- Protein C and Protein S activity levels
- Antithrombin activity assay
- Plasminogen
- Antiphospholipid antibody panel (done in mother)
- Factor V G1691A*** (Leiden mutation)
- Prothrombin G 20210A***

~ 1-2 ml of Blood**

**Blood Center of Wisconsin
***DNA-based assays
Tier 1 Laboratory Evaluation for Symptomatic Neonatal Thrombosis*

Perform at 3-6 Months

- Antiphospholipid antibody panel***
- Protein C and S activity levels
- Antithrombin activity assay
- Factor V G1691A (Leiden mutation)***
- Prothrombin G 20210A***

~ 1-2 ml of Blood**


**Blood Center of Wisconsin

***If not done in NICU
Tier 2 Laboratory Evaluation for Symptomatic Neonatal Thrombosis*

*Perform at 3-6 Months*

- MTHFR
- Lipoprotein (a)
- Homocysteine level
- Factor VIII Activity
- Factor IX Activity
- Factor XI Activity
- Factor XII Activity
- Plasminogen activity
- Heparin cofactor II

~ 6 ml of Blood (including prior evaluation)**


**Blood Center of Wisconsin

***If not done in NICU
Important Points Regarding Follow-up Evaluation*

• If initial NICU evaluation negative or not done
  – Follow-up with hematology warranted at 3-6 months

• If mutation or disorder identified or treatment initiated
  – Prompt follow-up evaluation with hematology

Take Home Messages

• Interpretation of diagnostic laboratory results should be approached with caution
• Test results outside the 95% confidence limit are not sufficient to define a disease
• Diagnosis of thrombophilia in neonates should be based on the presence of a positive clinical phenotype, family history, and of reproducible abnormal laboratory results

*Shoshana Revel-Vilk. The conundrum of neonatal coagulopathy.. American Society of Hematology
Take Home Messages

• Overdiagnosis and misdiagnosis may lead to administration of wrong and potentially harmful treatments for years

• Evaluation with hematologist will be tailored based on severity of thrombosis, type of thrombosis, family history, and clinical risk factors

*Shoshana Revel-Vilk. The conundrum of neonatal coagulopathy.. American Society of Hematology
Management of Neonatal Thrombosis

- Thrombolysis
- Anticoagulation
- Nitroglycerin
- Supportive care
- Surgery

**BMJ**

Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials

Gordon C S Smith and Jill P Pell

*BMJ* 2003;327;1459-1461
doi:10.1136/bmj.327.7429.1459
<table>
<thead>
<tr>
<th>Grade of Recommendation</th>
<th>Clarity of Risk/Benefit</th>
<th>Quality of Supporting Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1A Strong, high quality evidence</td>
<td>Benefits outweigh risks</td>
<td>Well-designed RCTs</td>
</tr>
<tr>
<td>1B Strong, moderate quality evidence</td>
<td>Benefits outweigh risks</td>
<td>RCTs with important limitations</td>
</tr>
<tr>
<td>1C Strong, low quality evidence</td>
<td>Benefits appear to outweigh risks</td>
<td>Observational studies or RCTs with major flaws</td>
</tr>
<tr>
<td>2A Weak, high quality evidence</td>
<td>Benefits balanced with risks</td>
<td>Well-designed RCTs or controlled trials</td>
</tr>
<tr>
<td>2B Weak, moderate quality evidence</td>
<td>Benefits balanced with risks with some uncertainty</td>
<td>RCTs with important limitations</td>
</tr>
<tr>
<td>2C Weak, low quality evidence</td>
<td>Uncertainty with benefits and risks</td>
<td>Observational studies and clinical experience</td>
</tr>
</tbody>
</table>

*Up to date, grading guide 2013
Management of Neonatal Thrombosis

Treatment should only occur at tertiary center that has proper neonatal, pediatric hematology, transfusion medicine, and pediatric surgical support*

Pediatric hematologists with experience in thrombosis manage pediatric patients with thrombosis (Grade 2C)*

Anticoagulant Therapy

Unfractionated Heparin (UFH)  LMWH

A-Antithrombin  FXa

Prothrombin
Thrombin

rTPA

Thrombolytic Therapy

Plasmin

Plasminogen
Thrombolytic Therapy

rTPA
Review of Case Series Using rTPA in Neonates *

- 6 case series and one literature review
- Total of 50 neonates
- 543-5060 grams
- 1998-2003
- Dosing ranged from bolus to low dose continuous infusion
- One death from bleeding
- 17% major and 26% minor hemorrhage

## rTPA Systemic Thrombolysis*

<table>
<thead>
<tr>
<th>Gestational Age</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 28-weeks</td>
<td>0.03 mg/kg/hour</td>
</tr>
<tr>
<td></td>
<td>0.06 mg/kg/hour</td>
</tr>
<tr>
<td>≥ 28-weeks</td>
<td>As above</td>
</tr>
<tr>
<td></td>
<td>0.1-0.5 mg/kg/hour for 6-12 hours</td>
</tr>
<tr>
<td></td>
<td>May repeat daily for 3-days</td>
</tr>
</tbody>
</table>

Low-Dose rTPA Protocol per Pediatric Coagulation Consortium*

- Dose escalation up to 0.24 mg/kg/hr
- Treat 48-96 hours or resolution of thrombus
- Infusion of 10 U/kg/hr of UFH to prevent proximal clot extension
- Effectiveness in neonates can be impaired due to lower plasminogen levels**
  - Administer 10-15 ml/kg FFP prior to starting therapy


Before rTPA Treatment
After rTPA Treatment
# Monitoring Thrombolytic Therapy

<table>
<thead>
<tr>
<th>Testing</th>
<th>When Performed</th>
<th>Levels Desired (if applicable)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imaging of thrombosis</td>
<td>Before treatment Every 12-24 hours during</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fibrinogen level</td>
<td>Before treatment 4-6 hours after start</td>
<td>Minimum of 100 mg/dL</td>
</tr>
<tr>
<td></td>
<td>Every 12-24 hours during</td>
<td>Supplement with cryoprecipitate</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelet count</td>
<td>Before treatment 4-6 hours after start</td>
<td>Minimum of 50-100 10^3/L</td>
</tr>
<tr>
<td></td>
<td>Every 12-24 hours during</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cranial imaging</td>
<td>Before treatment Daily</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coagulation testing</td>
<td>Before treatment 4-6 hours after start</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Every 12-24 hours during</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasminogen/D-dimers</td>
<td>Before treatment 4-6 hours after start</td>
<td>Adequate to achieve thrombolysis</td>
</tr>
<tr>
<td></td>
<td>Every 12-24 hours during</td>
<td></td>
</tr>
</tbody>
</table>
Anticoagulation

UFH

LMWH
Revised Dosing of UFH*,**

<table>
<thead>
<tr>
<th>Gestational Age</th>
<th>Loading Dose</th>
<th>Maintenance Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 28-weeks*</td>
<td>25 u/kg</td>
<td>15 u/kg/hour</td>
</tr>
<tr>
<td>28-37 weeks*</td>
<td>50 u/kg</td>
<td>15-20 u/kg/hour</td>
</tr>
<tr>
<td>&gt; 37-weeks*</td>
<td>100 u/kg</td>
<td>28 u/kg/hour</td>
</tr>
</tbody>
</table>

- Loading dose over 10 minutes
- Maintain an anti-Factor Xa level of 0.3 – 0.7 units/ml (PTT of 60-85 s)
- Check anti-Factor Xa level 4 hours after loading dose and 4 hours after each change in infusion rate
- ± antithrombin activity level

UFH and Antithrombin

Treatment

- Effectiveness dependent on adequate antithrombin levels
  - Neonates have low levels of antithrombin activity
- Heparin potentiates effect of antithrombin
- Inadequate antithrombin levels reduces effectiveness of heparin therapy
- Recommended doses reflect lower levels of antithrombin
Antithrombin

• Studies performed on neonates using either human or recombinant antithrombin for neonates on ECMO*
  – Some have demonstrated reduction in heparin dose with more consistent anticoagulation without risk for excessive bleeding
  – Bolus vs continuous infusions
  – Provide for antithrombin levels < 60%
  – Goal is for 60-100%

• Dosing
  – Units = \([\text{desired \%AT} - \text{baseline\%AT}] \times \text{weight (kg)}\)

1.4

*Antithrombin administration during pediatric ECMO. Buck. February 2013.
UFH
Complications

• Bleeding (1.9%)
  – Stop infusion
  – Start protamine if Anti-Factor Xa level > 0.8 u/mL or large overdose given

• Heparin-induced thrombocytopenia (very rare)
  – Drop in platelet count by 50% or persistently < 70-100,000/mm³ occurring 5-10 days after first exposure to heparin
LMWH

- Therapy has been effective in the NICU – subQ

- Retrospective study*
  - 16 neonates (1998-2006)
  - 71% of thromboembolic events resolved (complete or partial)

# LMWH
(Enoxaparin)

<table>
<thead>
<tr>
<th>Gestational Age</th>
<th>Dose*</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 28-weeks</td>
<td>1.25 mg/kg SQ q 12-hours</td>
</tr>
<tr>
<td>28-37-weeks</td>
<td>1.5 mg/kg SQ q 12-hours</td>
</tr>
<tr>
<td>&gt; 37-weeks</td>
<td>1.625 mg/kg SQ q 12-hours</td>
</tr>
</tbody>
</table>

- Goal of anti-FXa level of 0.5 to 1.0 U/ml when level checked 4-6 hours after 2nd dose (SQ injection)
- Goal of anti-FXA level of 0.5 – 0.8 U/ml when level checked 2-6 hours after SQ injection
- If infant with high hemorrhagic profile, use standard dosing
- ± antithrombin activity level, platelet count

LMWH
(dalteparin)

<table>
<thead>
<tr>
<th>Gestational Age</th>
<th>Dose*</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 28-weeks</td>
<td>100 U/kg SQ q 12-hours</td>
</tr>
<tr>
<td>28-37-weeks</td>
<td>125 U/kg SQ q 12-hours</td>
</tr>
<tr>
<td>&gt; 37-weeks</td>
<td>150 U/kg SQ q 12-hours</td>
</tr>
</tbody>
</table>

- Goal of anti-FXa level of 0.5 to 1.0 U/ml when level checked 4-6 hours after 2nd dose (SQ injection)
- Goal of anti-FXA level of 0.5 – 0.8 U/ml when level checked 2-6 hours after SQ injection
- If infant with high hemorrhagic profile, use standard dosing
- ± antithrombin activity level, platelet count

Before LMWH Treatment
After LMWH Treatment
LMWH Complications*,**,***

- 240 neonates
- Major bleeding
  - 13 of 240 (5%)
  - No major bleeds in premature neonates
- Minor side effects (Common)
  - Soreness from injection/catheter, induration, leakage, bruising


Large hematoma from previous insuflon catheter*

Anticoagulation

- **Heparin**
  - Requires IV access
  - Short term anticoagulation
  - 3 days to 3 weeks
  - If surgery pending

- **LMWH**
  - Anticoagulant of choice in NICU
  - Insuflon® catheter
  - Fewer side effects?
  - Long term anticoagulation
Contraindications to Thrombolytic/Anticoagulation Therapy*

• Absolute
  – CNS surgery or ischemia (including birth asphyxia) within ten days
  – Active bleeding
  – Invasive procedures within three days
  – Seizures within 48-hours

Contraindications to Anticoagulation/Thrombolytic Therapy*

- Relative
  - Platelet count < $50 \times 10^4$/microliter (100 $\times 10^4$/microliter for ill neonates)
  - Fibrinogen concentration < 100mg/dL
  - Severe coagulation deficiency
  - Hypertension

Clinical Protocols
If you don’t absolutely need it, remove it!
Management of Central Venous Catheter Thrombosis*

• Option 1: CVADs or UVCs with confirmed thrombosis should be removed after 3-5 days of therapeutic anticoagulation (Grade 2C)

• Option 2: Supportive care option
  – Remove catheter
  – Radiologic monitoring for extension
  – If extension occurs, start anticoagulation (Grade 2C)

• Anticoagulate between 6 weeks to 3 months (Grade 2C)

• No thrombolysis unless critical compromise of organ or limb (Grade 2c)

Management of Vascular Spasm*

- Is the arterial line necessary?
  - If no, remove it!
- UACs-warm contralateral extremity
- After removal of UAC or PAL, may have persistent vasospasm or small clots in distal end arteries
  - Topical nitroglycerin
    - 4-mm/kg dose of 2% ointment (0.2-0.5 mcg/kg)
    - Potential side effect
      - Hypotension

*Baserga et al. The use of topical nitroglycerin ointment to treat peripheral tissue ischemia secondary to arterial line complications in neonates. J of Perinatology. 2002.
Management of Peripheral Arterial Catheter-Related TE Event*,**, 

- Immediate removal of catheter (Grade 2B)
  - UFH with or without rTPA (Grade 2C)
  - Surgical thrombectomy and microvascular repair with heparin therapy (Grade 2C)


Management of Femoral Artery Thrombosis*

• Acute femoral artery thrombosis
  – IV UFH (Grade 1B)
    • Conversion to LMWH or continuation of therapy for 5-7 days (Grade 2C)

• Limb-threatening or organ-threatening femoral artery thrombosis (Grade 1C)
  – IV UFH
    • If treatment fails, thrombolysis
    • If contraindication to thrombolysis, surgery

Management of Arterial Ischemic Stroke*

First AIS and ongoing cardioembolic source

YES

Anticoagulation (Grade 2C)

NO

Supportive Care (Grade 2C)

Recurrent AIS

Anticoagulation or Aspirin (Grade 2C)

Management of CSVT*

Confirmed diagnosis by MRI and MRV

- No hemorrhage, start UFH or LMWH (Grade 2C)
- Hemorrhage present, no treatment (anticoagulation)
  - Repeat MRV in 5-7 days and if thrombus propagating, start UFH or LMWH (Grade 2C)

Repeat MRI and MRV in 6-weeks for vessel recanalization. If complete, stop therapy. If not, consider 6-more weeks of treatment (Grade 2C)

Management of Renal Vein Thromboses*

• Unilateral (Grade 2C)
  – Absence of renal impairment or extension into the IVC
    • Supportive care with radiologic monitoring for extension
    • Anticoagulation (6 weeks to 3 months)

• Unilateral (Grade 2C)
  – Extends into the IVC
    • Anticoagulation for 6 weeks to 3 months

• Bilateral (Grade 2C)
  – Evidence of renal impairment
    • Anticoagulation or initial rTPA followed by anticoagulation

Purpura Fulminans*

- 10-20 ml/kg of FFP q 6-12 hours
- Protein C concentrate at 20-60 units/kg until lesions resolve (Grade 1A)
- If homozygous protein C deficiency in neonates diagnosed, after stabilization:
  - LMWH (Grade 1C)
  - Protein C replacement (Grade 1B)
  - Liver transplantation (Grade 1C)

Future Goals

Neonatal Thrombosis Referral Center
Levine Children’s Hospital
Charlotte, NC
*Designated NICU/PICU beds
*Neonatal protocols
*Peds Hematology
Follow up clinic
Future Goals

• Safer (tested) and easier to administer neonatal anticoagulation

• Enhanced databases specific for types of thromboses and patient populations

• Specific referral centers for neonatal coagulation disorders
Conclusions

• Lack of randomized trials addressing neonatal thromboses force neonatologists to base decisions on limited evidence

• Treat effectively without causing harm
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