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Two Waterfalls Run to Completion: Describes process in test tube

HMXK, PK, XII

\[ \text{XI} \quad \Phi \quad \Phi \quad \Phi \]

"Intrinsic Pathway"

\[ \text{XII} \quad \Phi \quad \Phi \quad \Phi \]

"Extrinsic Pathway"

\[ \text{X} \quad \Phi \quad \Phi \quad \Phi \]

"Common Pathway"

Thrombin

Fibrin

V:PL

II (Thrombin)

Fibrinogen
Intrinsic Pathway:

Partial Thromboplastin Time (PTT)

Extrinsic Pathway:

Prothrombin Time (PT)

In vivo Hemostasis Results in a Clot Confined to the Site of Injury

- Goal: Formation of an impermeable plug at vessel injury
  - Fibrin
  - Platelets
- Control mechanisms prevent spread of clot beyond the site of injury
  - Localization of procoagulant substances at the site of injury
  - Managed by specific cell surfaces
  - Prevent spreading through vascular system

New Feedback Model of Coagulation Better Reflects *in vivo* Hemostasis

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Developmental Hemostasis is a Normal Physiologic Process

- Dynamic, evolving system
- Different in infancy and early childhood than adults
- Hemostatic protein concentrations are dependent on gestational and postnatal age
  - Do not cross the placental barrier
  - Synthesized by the fetus starting ~10 weeks gestation
  - Generally increase with increasing gestational age
- Appropriate reference ranges are critical to interpreting lab evaluations of neonates with bleeding or clotting

-Chalmers. Arch Dis Child Fetal Neonatal Ed. 2004
Decreased Thrombotic Potential in Neonates

- Prolonged PT and aPTT
- Decreased vitamin K-dependent factors
  - FII, FVII, FIX, FX
  - 50% of normal adult values at term
  - Increases to near normal adult levels by 6 months
  - Lower in preterm infants
- Decreased FXI
- (Decreased FXII: prolongs PTT but does not result in clinical bleeding)

Increased Thrombotic Potential in Neonates

- Decreased vitamin K-dependent anticoagulants: Protein C, Protein S
- Decreased Antithrombin III
- Decreased Plasminogen
- Only Protein C remains low beyond 6 months

Neonates Have Bleeding Times in Adult Range

- Platelets
  - Quantitatively at adult level
  - Qualitatively hyporeactive compared to adults
- von Willebrand Factor
  - Elevated in neonates
  - Presence of large multimers
- Factor VIII
  - At adult level
- Increased viscosity
  - Elevated hematocrit
  - Increased RBC size
Overall Hemostatic Potential in Neonates: A Fine Balance

- Generally in equilibrium with few bleeding or clotting problems in healthy newborns
- Protected against thrombosis:
  - Delayed and decreased thrombin generation
- Protected against bleeding:
  - Delayed thrombin inhibition
  - Decreased plasmin generation
- Sick newborns, however, have a disturbance in this balance
  - Tendency to thrombosis

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Bleeding Neonates: Ill or Well?: Acquired Causes Most Common

- Acquired coagulopathy: More likely in ill infants
  - Review obstetric and neonatal course
  - DIC
    - Acidosis, RDS, meconium aspiration, hypothermia, NEC, sepsis, exchange transfusion, malignancy, etc
- Inherited bleeding disorders or immune thrombocytopenias: more often in well infants
  - Review family history of bleeding
  - Immune thrombocytopenia (ITP) or Neonatal alloimmune thrombocytopenia (NAIT)
### Initial Lab Evaluation for Bleeding

<table>
<thead>
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<th>Conditions</th>
<th>PT</th>
<th>APTT</th>
<th>Fibrinogen</th>
<th>Platelets</th>
<th>Other Testing</th>
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<td>Inherited Disorders</td>
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<td>Nl</td>
<td>Nl</td>
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<td>FXIII deficiency</td>
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<td>FXIII assay</td>
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<tr>
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<tr>
<td>Immune</td>
<td>Nl</td>
<td>Nl</td>
<td>Nl</td>
<td>↓</td>
<td>NAUT Testing</td>
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<tr>
<td>DIC</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↓</td>
<td>D-Dimers</td>
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<tr>
<td>vK K deficiency</td>
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<td>↑</td>
<td>Nl</td>
<td>Nl</td>
<td>FII, VII, IX, X</td>
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<tr>
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<td>↑</td>
<td>Nl</td>
<td>Nl</td>
<td>Factor activities</td>
</tr>
</tbody>
</table>

*Abnormalities relative to age-appropriate normals

### The Workup Continues…

- **False positive evaluations**
  - Need to interpret lab results in context of developmental hemostasis
  - Pediatric reference ranges
- **False negative evaluations**
  - Often miss mild disorders in newborns
    - Mild hemophilia, type 1 and 2 von Willebrand disease
  - Platelet function disorders not evaluated
  - Rare bleeding disorders

### Sites of initial bleeding episodes, mode of delivery and age of diagnosis in babies with haemophilia diagnosed before the age of 2 years: a report from the Centers for Disease Control and Prevention’s (CDC) Universal Data Collection (UDC) project

*Haemophilia* (2009), 15, 1281-1290

- **Prospective cohort study**
  - 580 children with hemophilia, diagnosed age 0-2y
    - 80% Hemophilia A (FVIII deficiency)
    - 68% vaginal delivery
    - 394 had bleeding in first 2 years

Kulkarni R et al., Haemophilia, 2009
Sites of Bleeds in Infants with Hemophilia of All Severities

- Circumcision: 27% (90% in first month of life)
  - Infants with no family history: 43% of bleeds
- Bleeding in the head: 18% (40%)
  - 36% intracranial
  - Seen in Severe (19%), Mod (16%), Mild (20%)
- Bleeding from puncture wounds (ex. heel stick, IM): 17% (21.5%)
- Oral mucosa: 9.6% (1%)
- Joint: 6.2% (0.5%)
- 17 delivery-related ICH: 16 vaginal (2 assisted), 1 cesarean section (P=0.2)

Important Role of Newborn Health Care Providers

- Goal: To diagnose inherited bleeding diatheses at earlier age
  - 15-33% diagnosed in newborn period
- Bleeding symptoms in neonates seem to differ from those in older patients
- Most symptoms iatrogenic and trauma induced
  - Potentially reduced by identifying maternal carrier status
- Lack of bleeding with circumcision does not rule out an inherited bleeding disorder

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Dramatic Increase in Venous Thromboembolism in Children’s Hospitals in the United States From 2001 to 2007

- 70% increase from 34/10,000 to 58/10,000 hospital admissions\(^1\)
  - Pediatric Health Information System database from Child Health Corporation of America’s 41 free-standing children’s hospitals
  - 10X higher than Canadian report from 1994\(^2\)

- Highest rates in neonates and teens
  - Neonates increased from 45 to 75 VTE/10,000 hospital admissions
  - Teens 65 to 95 VTE/10,000 hospital admissions

- Children with complex chronic conditions

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Increasing VTE: Advances in Care of Critically Ill Children?

- Improved diagnostic tests or increased recognition
- Survival of medically complicated children
  - Cardiac disease
  - Malignancy
  - Rheumatologic illnesses
  - Gastrointestinal - inflammatory bowel disease, short gut
  - Renal – nephrotic syndrome
- More intense therapies and interventions
  - Chemotherapy
  - Cardiac surgeries
  - Central lines
  - TPN
  - Neonatal and pediatric intensive care

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Non-CNS Thrombosis in Neonates

- 50% of neonatal TE is arterial
  - Mainly catheterization related (femoral, umbilical, peripheral arteries)
  - Rarely spontaneous, mostly aorta
- >80% of VTE: central venous lines
  - UVC-related VTE incidence estimated at 18%
- Renal vein thrombosis
  - Most common non-catheter related VTE
  - 2.2/100,000 live births
  - Associated with sepsis, shock, polycythemia, CHD, maternal diabetes, dehydration
- Portal vein thrombosis
  - 75% UVC-related

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\(^1\)Raffini, Pediatrics, 2009
\(^2\)Andrew, Blood, 1994

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Saracco, Thromb Res. 2009
Andrew MA, Am Soc Hematol Ed. 2001
Presence of Indwelling Line is Most Important TE Risk Factor in Neonates

- Damage to endothelium
- Activation of coagulation
- Disrupted blood flow in narrow vessels
- TPN infusions (endothelial cell damage)
- Thrombogenic catheter material
- Sicker infants requiring catheters


Role of Thrombophilic Risks in Neonatal TE is Poorly Understood

“Common” Genetic Thrombophilia Risks

- Antithrombin deficiency
- Protein C deficiency
- Protein S deficiency
- Factor V Leiden (resistance to activated protein C) mutation
- Prothrombin 20210 mutation

Antithrombin Deficiency

- Mostly autosomal dominant inherited
- Homozygous deficiency: usually fatal in utero, or presents in 1st decade
- Prevalence estimates from 1 in 500 to 1 in 5000
- Levels in infants ~50-60% of normal adult values and rise to normal by 6 months
- Acquired deficiency: nephrotic syndrome and heparin use

Patnaik. Haemophilia. 2008
Protein C and S Deficiencies

- Mostly autosomal dominantly inherited
- Homozygous deficiency:
  - Neonatal DIC and purpura fulminans
- Carrier rate: ~1 in 200 to 1 in 500
- Levels in infants as low as ~20-30% of adults
  - Protein S at adult level by 6 months
  - Protein C at 50% at 6 months reaching adult levels by late teen years
- In the setting of acute clot, PC/PS are consumed

Goldenberg. Haemophilia. 2008
ten Kate. Haemophilia. 2008

Factor V Leiden

- R506Q mutation in Factor 5 gene
- Factor V is resistant to inactivation by the activated protein C and S complex
- Most common inherited prothrombotic risk factor in Northern Europeans
- ~5/100: heterozygous carrier rate

Andrew et al. Thromboembolic Complications during Infancy and Childhood. 2002

Prothrombin 20210 Mutation

- G20210A mutation in the 3’ untranslated region of the prothrombin mRNA
- ~2% in the Caucasian population
- Heterozygous adults have increased prothrombin levels
- Unclear if this is true in children given lower levels of prothrombin
  - 50% of adult levels at birth, 80% by 3 months, but does not increase to adult levels until late teens

Andrew et al. Thromboembolic Complications during Infancy and Childhood. 2002
**MTHFR Mutations NOT Associated with Thrombosis**

- TE in patients with homocysteinuria
  - Deficiency of cystathione β-synthase
  - Marked elevations of homocysteine (>100)
- Moderate increases in homocysteine associated with TE
  - Methylene tetrahydrofolate reductase (MTHFR) gene polymorphisms may increase homocysteine
    - Not associated with thrombosis
- Consider testing homocysteine levels

*Raffini. Br J Haematol. 2009*

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**Does Testing for Thrombophilia:**

1. Improve clinical outcome?
2. Guide therapy (duration or intensity)?
3. Guide or improve secondary prophylaxis?
4. Alter anticipatory guidance as infant ages?
   - Hormone therapy
   - Pregnancy
   - Lifestyle modifications

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**Evaluating the Risks of VTE**

- Risk of first VTE in children: 1 in 100,000
- Risk of first VTE in adults: 1-2 in 1,000
- Relative risks in patients with defects:
  - Heterozygous PC, PS, AT deficiency: 24-30X
  - Heterozygous FVL, 20210: 5-8X
- Bleeding on anticoagulation: 0.5-1% risk per year
- 8% risk of recurrence in children
- Relative risks for recurrent VTE in patients with defects:
  - All individual defects: 3-5X
  - Combined defects: 10X

Benefits of Testing are Limited

- No convincing evidence in adults that testing improves outcomes
- Testing in adults with VTE does NOT reduce the incidence of recurrence
- Evidence lacking in children except in:
  - Homozygous protein C or S deficiency (acute and chronic rx)
  - Antithrombin deficiency: inherited or acquired
- Duration of therapy is rarely affected except in:
  - ”High-risk” defects: homozygous FVL or >1 congenital risk factor
    - May benefit from long-term anticoagulation
  - Antiphospholipid antibody syndrome (APLS)
    - Indefinite anticoagulation

Downsides of Testing

- Large volume of blood from small baby
- Misinterpreting lab results
  - Developmental hemostasis
  - Acquired deficiencies (acute clot or warfarin)
- Psychosocial effects
  - Anxiety
  - False reassurance in negative workup
- Cost ($2,360 at UCSF)
  - Not cost effective in determining duration of therapy in all-comers with pediatric TE
- Genetic testing in minors
  - Risks of discrimination

Risk of Thrombosis: A Continuum

- Severity of deficiencies can vary
  - May depend on mutation
- Understanding of how various degrees of deficiencies affect coagulation is unclear
- Other genetic or acquired factors may alter thrombotic risk
  - Compound defects have increased risk
- Thrombophilic traits serve as risk factors
- Further research is needed
Non-Urgent, Stepwise Approach to Evaluating Neonates with VTE

- Most VTE in this group are due to acquired risk factors and are TRANSIENT
- Limited initial testing
  - Protein C and S levels ONLY if Purpura Fulminans
  - Antithrombin level as it will affect the efficacy of anticoagulant treatment (heparin and low molecular weight heparin)
- Reserve further testing for later
  - Consider antiphospholipid antibody testing in mother if history is suggestive
  - Genetic risks (FVL, PT20210), could test parents
  - After counseling the parents and patient on potential ramifications and utility

Saracco. Thromb Res. 2009

Summary

- Classic “cascade” model of coagulation is an incomplete description of the in vivo process
- Evolving model is an integrated system of enzyme complexes with amplification and regulation loops
- The neonatal hemostatic system differs in both its pro-and anticoagulant properties
- Bleeding and thrombosis in newborns are most commonly due to acquired risk factors
  - Evaluation needs to take into account developmental hemostasis
- Inherited bleeding disorders may be missed by initial screening tests
- Thrombophilia testing should not be “reflexive” but must take into account:
  - The utility of the test for making therapeutic decisions
  - The long term impact of the test on the family
  - Neonatal norms and the clinical setting (TE, anticoagulation)

Select References