Pharmacist Objectives

• Compare and contrast differences between adult and pediatric anticoagulation management
• Discuss high-risk pediatric populations and indications for anticoagulation
• Evaluate available anticoagulant agents and use of them in the pediatric population
• Given a patient case, select a treatment regimen and monitoring plan
Technician Objectives

- Identify anticoagulants commonly used in pediatric patients
- Discuss different dosing of anticoagulants in pediatrics compared to adults
- Recognize available dosage forms and available strengths of anticoagulants used in pediatrics
Disclosure

- I have nothing to disclose related to the content of this presentation.
Patient Case

- HG is a 14 year old caucasian female who presents to the emergency room with chief complaint of lower leg pain and swelling.
- She denies any leg injury, shortness of breath or chest pain.
- You are an inpatient clinical pharmacist responsible for providing recommendations to the inpatient medical team for comprehensive patient medication management.
Patient Case Continued...

• Past Medical History:
  ▫ Diagnosed with Polycystic Ovarian Syndrome (PCOS) at age 12
  ▫ NKDAs
  ▫ Immunizations: up to date

• Current medications:
  ▫ Ethinyl estradiol 0.03 mg/desogestrol 0.15 mg daily (Started approximately 2 years ago)

• Prescription Insurance
  ▫ Blue Cross Blue Shield of Alabama
Patient Case Continued...

- **Family History:**
  - Maternal grandfather – hypertension, dyslipidemia
  - Paternal grandfather – type 2 diabetes mellitus (T2DM), prostate cancer
  - Mother – hypertension, dyslipidemia
  - Father – T2DM, dyslipidemia
  - No known clotting disorders

- **Social History**
  - 8th grader
  - Lives with mother, father, and brother (11)
  - Denies smoking, alcohol and recreational drug use
Patient Case Continued...

- **Review of Systems:**
  - General: (+) fatigue, (-) fever
  - CV/Pulm: (-) shortness of breath, chest pain
  - Ext: (+) tenderness, (+) LLE swelling, (-) discoloration

- **Physical Exam:**
  - RR 18 resp/min, HR 122 bpm, BP 150/95 mm Hg, Temp 99.1°F, O₂ sat 98% RA
  - 80 kg, 160 cm, BMI 32 kg/m²
  - Left calf warm to touch and tender, LLE with warmth and swelling, normal ROM and pulses
Patient Case Continued...

- CBC: WNL
- SCr: 0.8 mg/dL
- Doppler ultrasound: Acute deep vein thrombosis (DVT) of left popliteal vein.
- PT/INR: 10.9 sec / 1.1
Question 1

Based on HG’s symptoms and confirmed DVT via ultrasound, she is admitted to begin anticoagulation. Which of the following would be considered appropriate for initial treatment of HG’s DVT?

a. Warfarin  
b. Enoxaparin  
c. Rivaroxaban  
d. Dabigatran
Treatment of Venous Thromboembolism (VTE) in Children

- CHEST Guidelines
  - Standards primarily derived from adult literature
  - Majority of recommendations graded as “weak”

- Acute therapy (At least 5 days)
  - Unfractionated heparin (UFH)
  - Low molecular weight heparin (LMWH)

- Ongoing therapy
  - Vitamin K antagonists

Question 1

Based on HG’s symptoms and confirmed DVT via ultrasound, she is admitted to begin anticoagulation. Which of the following would be considered appropriate for initial treatment of HG’s DVT?

a. Warfarin
b. Enoxaparin
c. Rivaroxaban
d. Dabigatran
Unfractionated Heparin (UFH)

• Loading dose
  ▫ Neonates and children: 75 units/kg

• Maintenance dose
  ▫ Less than 1 year old: 28 units/kg/hr
  ▫ 1-12 years old: 20 units/kg/hr
  ▫ Greater than 12 years old: 18 units/kg/hr

• Prophylaxis dose
  ▫ 10 units/kg/hr
UFH Pharmacokinetics in Pediatrics

- Increased volume of distribution
- Increased clearance
- Lower percentage of anti-thrombin
- Reduced capacity to generate thrombin

UFH Therapeutic Monitoring

- Activated partial thromboplastin time (aPTT)
  - Range that correlates with protamine titration range of 0.2 to 0.4 unit/mL

- Anti-Xa
  - Therapeutic goal = 0.35 to 0.7 units/mL*

*Obtain 4 hours after loading dose administration and 4 hours after any infusion rate change

# UFH Dosage Adjustment by aPTT

<table>
<thead>
<tr>
<th>aPTT (seconds)</th>
<th>Recommended Dosage Adjustment</th>
</tr>
</thead>
</table>
| Less than 50   | Bolus 50 units/kg  
Increase drip by 10%                                                |
| 50 - 59        | Increase drip by 10%                                             |
| 60 - 85        | No change                                                        |
| 86 - 95        | Decrease drip by 10%                                             |
| 96 - 120       | Hold drip for 30 minutes  
+ Decrease drip by 10%                                                 |
| Greater than 120| Hold drip for 1 hour  
+ Decrease drip by 15%                                                 |

Roach. Stroke. 2008; 2644-91
# UFH Dosage Adjustment by Anti-Xa

<table>
<thead>
<tr>
<th>Anti Xa Level (units/mL)</th>
<th>Recommended Dosage Adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than 0.2</td>
<td>Bolus 75 units/kg</td>
</tr>
<tr>
<td></td>
<td>Increase drip by 4 units/kg/hr</td>
</tr>
<tr>
<td>0.2 - 0.29</td>
<td>Bolus 40 units/kg</td>
</tr>
<tr>
<td></td>
<td>Increase drip by 2 units/kg/hr</td>
</tr>
<tr>
<td>0.3 – 0.7</td>
<td>No change</td>
</tr>
<tr>
<td>0.71 – 0.8</td>
<td>Decrease drip by 2 units/kg/hr</td>
</tr>
<tr>
<td>0.81 – 0.99</td>
<td>Hold drip for 1 hour</td>
</tr>
<tr>
<td></td>
<td>+ Decrease drip by 2 units/kg/hr</td>
</tr>
<tr>
<td>Greater than or equal to 1</td>
<td>Hold drip for 1 hour</td>
</tr>
<tr>
<td></td>
<td>+ Decrease drip by 3 units/kg/hr</td>
</tr>
</tbody>
</table>
Question 2

The inpatient team decides to begin therapy with enoxaparin and asks for guidance in dosing. Which would be the most appropriate recommendation?

a. 40 mg twice daily
b. 80 mg once daily
c. 120 mg once daily
d. 80 mg twice daily
# Low Molecular Weight Heparin (LMWH)

<table>
<thead>
<tr>
<th>Age</th>
<th>Enoxaparin Treatment</th>
<th>Enoxaparin Prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premature less than 1 month:</td>
<td>2mg/kg/dose subQ every 12 hours</td>
<td>0.75mg/kg/dose subQ every 12 hours</td>
</tr>
<tr>
<td>Full term less than 1 month</td>
<td>1.7mg/kg/dose subQ every 12 hours</td>
<td>0.75mg/kg/dose subQ every 12 hours</td>
</tr>
<tr>
<td>1 to 2 months:</td>
<td>1.5mg/kg/dose subQ every 12 hours</td>
<td>0.75mg/kg/dose subQ every 12 hours</td>
</tr>
<tr>
<td>2 months to less than 14 years:</td>
<td>1mg/kg/dose (Max: 150mg/dose) subcutaneous every 12 hours</td>
<td>0.5mg/kg/dose subQ every 12 hours</td>
</tr>
<tr>
<td>Greater than or equal to 14 years:</td>
<td>1mg/kg/dose (Max: 150mg/dose) subcutaneous every 12 hours - or- 1.5mg/kg/dose (Max: 225mg/dose) subcutaneous every 24 hours</td>
<td>0.5mg/kg/dose (Max: 30mg/dose) subcutaneous every 12 hours - or- 40mg subcutaneous every 24 hours (*May increase by 30% in obese patients)</td>
</tr>
</tbody>
</table>

(*May increase by 30% in obese patients*)
Question 2

The inpatient team decides to begin therapy with enoxaparin and asks for guidance in dosing. Which would be the most appropriate recommendation?

a. 40 mg twice daily
b. 80 mg once daily
c. 120 mg once daily
d. 80 mg twice daily
Question 3

After beginning enoxaparin therapy, which of the following is the most appropriate recommendation in regards to monitoring anti-Xa levels for HG?

a. Draw anti-Xa 4 hours post first dose
b. Draw anti-Xa 4 hours post third dose
c. Draw anti-Xa 8 hours post third dose
d. Anti-Xa levels are not indicated per guidelines
LMWH Therapeutic Monitoring

<table>
<thead>
<tr>
<th>Anti-Xa</th>
<th>Treatment Range</th>
<th>Prophylactic Range</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.5 to 1 units/mL</td>
<td>0.1 to 0.3 units/mL</td>
</tr>
</tbody>
</table>

- Anti-Xa level should be obtained 4-6 hours after steady state injection

Monagle PM et al. *Chest* 2012; 141 (2 Suppl):e-737S-e801S.
Question 3

After beginning enoxaparin therapy, which of the following is the most appropriate recommendation in regards to monitoring anti-Xa levels for HG?

a. Draw anti-Xa 4 hours post first dose  
b. **Draw anti-Xa 4 hours post third dose**  
c. Draw anti-Xa 8 hours post third dose  
d. Anti-Xa levels are not indicated per guidelines
HG is terrified of having to receive enoxaparin injections, so the team asks your advice on initiating bridge therapy with warfarin. Which would be the best recommendation for HG’s warfarin?

a. Begin 5 mg daily following 5 days of enoxaparin
b. Begin 5 mg daily on Day 1 of enoxaparin
c. Begin 10 mg daily following 5 days of enoxaparin
d. Begin 10 mg daily on Day 1 of enoxaparin
### Warfarin

<table>
<thead>
<tr>
<th>Days</th>
<th>INR</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1</td>
<td>1 – 1.3</td>
<td>0.2 mg/kg/day (Max: 10mg)</td>
</tr>
<tr>
<td>Days 2 to 4</td>
<td>1.1 – 1.3</td>
<td>Repeat day 1 loading dose</td>
</tr>
<tr>
<td></td>
<td>1.4 – 1.9</td>
<td>50% of day 1 loading dose</td>
</tr>
<tr>
<td></td>
<td>2 – 3</td>
<td>50% of day 1 loading dose</td>
</tr>
<tr>
<td></td>
<td>3.1 – 3.5</td>
<td>25% of day 1 loading dose</td>
</tr>
<tr>
<td></td>
<td>&gt; 3.5</td>
<td>Hold until INR is &lt;3.5 then restart at 50% decreased dose</td>
</tr>
<tr>
<td>≥ 5 Days</td>
<td>1.1 – 1.4</td>
<td>Increase by 20% of dose</td>
</tr>
<tr>
<td></td>
<td>1.5 – 1.9</td>
<td>Increase by 10% of dose</td>
</tr>
<tr>
<td></td>
<td>2 – 3</td>
<td>No change</td>
</tr>
<tr>
<td></td>
<td>3.1 – 3.5</td>
<td>Decrease by 10% of dose</td>
</tr>
<tr>
<td></td>
<td>&gt;3.5</td>
<td>Hold until INR is &lt;3.5 then restart at 20% decreased dose</td>
</tr>
</tbody>
</table>

Monagle PM et al. *Chest* 2012; 141 (2 Suppl):e-737S-e801S.
Warfarin Challenges in Pediatrics

- Decreased plasma levels of vitamin K-dependent clotting factors
- Vitamin K supplemented formula
- Low vitamin K concentrations in breastmilk
- Tablet formulation only
- Frequent monitoring required
- Poor compliance
Question 4

HG is terrified of having to receive enoxaparin injections, so the team asks your advice on initiating bridge therapy with warfarin. Which would be the best recommendation for HG’s warfarin?

a. Begin 5 mg daily following 5 days of enoxaparin
b. Begin 5 mg daily on Day 1 of enoxaparin
c. Begin 10 mg daily following 5 days of enoxaparin
d. Begin 10 mg daily on Day 1 of enoxaparin
Duration of Treatment

- **Idiopathic VTE**
  - 6 to 12 months

- **Secondary VTE**
  - Risk factor has resolved
    - 3 months
  - Ongoing but potentially reversible risk factors
    - Beyond 3 months until risk factor has resolved

- **Recurrent Idiopathic VTE**
  - Indefinite

- **Recurrent Secondary VTE**
  - Resolution of precipitating factor
    - No less than 3 months

New Oral Anticoagulants in Pediatric

- Direct thrombin inhibitor
  - Dabigatran

- Factor Xa Inhibitors:
  - Apixaban
  - Edoxaban
  - Rivaroxaban
Prevention of VTE in Pediatrics

- VTE nationally recognized as common preventable hospital acquired condition in adults
- Prevalence in pediatrics is on the rise
- More than 70 hospitals nationwide collaborating to evaluate risk factors in pediatrics
Pediatric VTE Risk Assessment Models

- Peds-Clot Clinical Decision Rule
- Raffini Risk Assessment Model (RAM)
Peds-Clot Clinical Decision Rule (PCDR)

- Positive blood stream infection
- Central venous catheter (CVC)
- Direct admission to ICU/NICU
- Hospitalization $\geq 7$ days
- Immobilization $\geq 72$ hours
- Oral contraceptive use

Raffini RAM

- Treatment algorithm for patients ≥14 years of age
- Risk factors
  - Altered mobility
  - Acute conditions
  - Chronic conditions
  - Historical Factors
- Prophylaxis recommendation based on risk stratification
  - Low risk: Early ambulation
  - At Risk: Early ambulation and mechanical prophylaxis
  - High Risk
    - 21 years or greater: Pharmacological prophylaxis
    - Less than 21 years: “Strongly consider” pharmacological prophylaxis

Research Areas of Interest in Pediatrics

• Ongoing trials evaluating safety and efficacy of newer oral anticoagulants in pediatrics
• Collaboration between pediatric institutions to determine risk factors for identification high risk patients
• Research indicating the benefit versus risk of pharmacological prophylaxis in pediatrics
Questions?