Heparin Induced Thrombocytopenia HIT with Thrombosis HITT
Bob Lipsy, Pharm.D., BCPS, FASHP

Incidence

• Estimated vary because data are based on either detection of antibodies or on true platelet activation and thrombocytopenia
• Varies by drug, underlying condition, dose?
  – Antibodies: Heparin 20%, LMWH 8%
  – Heparin and orthopedic surgery 20%, cardiopulmonary bypass 70%
  – True HIT 1-4% with therapeutic doses of heparin, 0.2-0.8% with post-operative LMWH
Why the Concern?

- Per year: 600,000 cases, 300,000 thrombosis, 90,000 deaths
- 20% of cases of thrombocytopenia are evaluated for HIT
- 30% of suspected cases of HIT had heparin discontinued
- If you do not treat 20-50% of patients with have a thrombosis
- 30-day mortality of 15.3% with HIT and 20.7% with HIT and thrombosis

Platelet Factor 4

- Stored in platelet granules and released after platelet activation
- Binds to glycosoaminoglycans on endothelial surfaces and heparin
- Heparin infusion increased plasma PF4 15-30 fold through displacement from endothelial surface
Pathophysiology

- Severe immune-mediated adverse drug reaction
- IgG, IgA, and IgM antibodies to a complex of platelet factor-4 (PF4) and heparin
  - Less than 10% of time only IgA and IgM are present
  - IgA and IgM do not cause platelet activation
- Antibody-activated platelets degranulate and release procoagulants
  - Serotonin
  - Histamine
  - ADP

Pathophysiology

- Other procoagulant effects include increases in
  - Thromboxane
  - Ca2+ influx
  - Prothrombotic phospholipids
  - thrombin
- Antibody-coated platelets are cleared by the reticuloendothelial system
- Full removal takes approximately 100 days
Clinical Signs

- Thrombosis
  - Venous: 4 times as likely vs. arterial, associated with surgery, DVT (extensive, bilateral) PE, central venous catheter, and adrenal veins comprise 50% of clots
  - Arterial: aorta, femoral arteries, associated with cardiopulmonary bypass
- Skin lesions at injection site (necrosis)
- Systemic reaction following bolus
- Abdominal pain, hypotension, fever = adrenal infarct

Platelet Monitoring

- ACCP: High risk (heparin post-op) or intermediate risk (heparin for medical or obstetrical reasons or LMWH post-op)
- High risk: before and QOD for 14 days
- Intermediate: before and every 2-3 days for 14 days
- Heparin in last 100 days: before and 24 hours later
Other Causes of Platelet Declines

- Heparin administration (non-immune) 30%
- Surgery 30% resolves in 6 days
- Angioplasty with a IIb-IIIa inhibitor
- Disseminated intravascular coagulation, sepsis, multiorgan system failure

The 4Ts Assessment Point System

<table>
<thead>
<tr>
<th>Category</th>
<th>2 Points</th>
<th>1 Point</th>
<th>0 Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombocytopenia</td>
<td>&gt; 50% fall or nadir &lt; 100-150 x 10⁹ cells/L</td>
<td>30-50% fall or nadir of 100-150 x 10⁹ cells/L</td>
<td>&lt; 30% fall or nadir of &gt;150 x 10⁹ cells/L</td>
</tr>
<tr>
<td>Timing of platelet count fall</td>
<td>Days 5-10, day 1 if heparin exposure within past 30 days</td>
<td>Beyond day 10 or unclear (but fits with HIT)</td>
<td>No recent/current heparin use</td>
</tr>
<tr>
<td>Thrombosis or other sequelae</td>
<td>Thrombosis, skin necrosis, or acute systemic reaction after heparin bolus</td>
<td>Progressive, recurrent, or silent thrombosis, erythematous skin lesions</td>
<td>None</td>
</tr>
<tr>
<td>Other cause for thrombocytopenia</td>
<td>None evident</td>
<td>Possible</td>
<td>Definite</td>
</tr>
</tbody>
</table>
Laboratory Diagnosis

- Antibody presence: antigen assay, enzyme-linked immunoabsorbed assay (ELISA)
  - Highly sensitive 99% NPV
- Platelet Activation Tests: serotonin release assay (gold standard, highly specific), heparin-induced platelet aggregation, platelet aggregometry
- Should use both tests in combination

Management

- Stop offending agent
- Stop warfarin if started
  - Reversal has been recommended 1-2 mg vitamin K
- Do not start warfarin until platelets have recovered
  - > 150,000
- Start an alternative anticoagulant
  - 30-50% of patients with HIT and no thrombosis had a thrombosis after stopping heparin and not starting another anticoagulant
  - New thrombosis awaiting laboratory results 6.1% vs. 0.6%
## Alternative Anticoagulants

<table>
<thead>
<tr>
<th>Anti-coagulants</th>
<th>Patients #</th>
<th>Control Group #</th>
<th>Disorder</th>
<th>Composite Endpoint %</th>
<th>Major Bleeding %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Argatroban</td>
<td>418</td>
<td>Historic 185</td>
<td>Mixed</td>
<td>28.0 (41.5)</td>
<td>5.3 (6.1)</td>
</tr>
<tr>
<td>Argatroban</td>
<td>304</td>
<td>Historic 193</td>
<td>Mixed</td>
<td>25.6</td>
<td>3.1 (11.1)</td>
</tr>
<tr>
<td>Argatroban</td>
<td>390</td>
<td>Historic 98</td>
<td>Acutely III</td>
<td>38.8</td>
<td>8.2 (2.2)</td>
</tr>
<tr>
<td>Argatroban</td>
<td>121</td>
<td>Historic 26</td>
<td>CAD</td>
<td>30</td>
<td>4</td>
</tr>
</tbody>
</table>

## Alternative Anticoagulants

<table>
<thead>
<tr>
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<th>Major Bleeding %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lepirudin</td>
<td>112</td>
<td>Historic 120</td>
<td>Mixed</td>
<td>30.9</td>
<td>12.9</td>
</tr>
<tr>
<td>Lepirudin</td>
<td>71</td>
<td>Historic 120</td>
<td>Mixed</td>
<td>25.4</td>
<td>9.9</td>
</tr>
<tr>
<td>Lepirudin</td>
<td>25</td>
<td>PCIs</td>
<td>8</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Bivalirudin</td>
<td>52</td>
<td>PCI</td>
<td>4</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>
Argatroban

- Synthetic direct thrombin inhibitor
- Does not require ATIII
- Approved for thrombosis prophylaxis or treatment and PCI
- 1-2 mcg/kg/min IV infusion,
  - 0.5 mcg/kg/hr in moderate hepatic impairment
  - CrCl 45-60 50%, 30 to 44 30%, 15-29 15%
- Monitor aPTT 1.5 to 3 times normal, max 100 sec. Check at 2 hours

Argatroban

- Hydroxylation and aromatization by P450 CYP3A4/5
- Terminal half-life 39 to 51 minutes
- Direct thrombin inhibition effects aPTT, ACT, PT/INR, TT (Target INR 3-4 with warfarin while on argatroban)
Lepirudin

- Leach protein hirudin
  - recombinant (rDNA) hirudin
  - directly inhibits thrombin
  - not dependent on ATIII
  - anticoagulant effect is dose dependent
  - metabolized (hydrolysis) 45%
  - unchanged in urine 35%
  - T1/2 1.3 hours

Lepirudin

- 0.4 mg/kg bolus 10-15 sec, infusion 0.15 mg/kg/hr
  (0.1 mg/kg/hr, no bolus) No bolus is currently recommended unless life or limb threatening thrombosis
- aPTT ratio 1.5 to 2.5
- Do not start if aPTT over 2.5
- Adjust by aPTT at 4 hours
  - aPTT > 2.5 stop 2 hrs and restart at 50%
  - aPTT < 1.5 increase by 20%
- Decrease dose in renal dysfunction or with thrombolytics
- Antilepirudin antibodies 50%, anaphylaxis 0.2%
Bivalirudin

- Direct thrombin inhibitor
- IV bolus 0.75 mg/kg, followed by 1.75 mg/kg/hr x 4 hours followed by 0.2 mg/kg/hr
  - Hepatic dysfunction 0.14 mg/kg/hr
  - Renal dysfunction CrCl 30-60 0.1 mg/kg/hr, CrCl <30 0.05 mg/kg/hr
  - Hepatic and renal dysfunction 0.03-0.05 mg/kg/hr
  - aPTT 1.5 to 2.5 x nl
  - 50% of lepirudin ABs recognize bivalirudin
  - Target INR 5 with warfarin.

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<table>
<thead>
<tr>
<th>Variables</th>
<th>Immune HIT</th>
<th>Non-immune</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency</td>
<td>1-3%</td>
<td>20-70%</td>
</tr>
<tr>
<td>Reduction in PLT count</td>
<td>Moderate or severe</td>
<td>Mild</td>
</tr>
<tr>
<td>Time from initiation of heparin</td>
<td>5-14 days up to 3 weeks 1 day with recent exposure</td>
<td>&lt; 5 days</td>
</tr>
<tr>
<td>Antibodies present</td>
<td>Yes</td>
<td>Absent?</td>
</tr>
<tr>
<td>Platelet activation present</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Risk of thrombosis</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>Management</td>
<td>Discontinue heparin, administer alternative anticoagulant</td>
<td>Observation</td>
</tr>
</tbody>
</table>
THROMBOEMBOLIC DISORDERS: VENOUS THROMBOEMBOLISM PREVENTION AND HEPARIN-INDUCED THROMBOCYTOPENIA

Samantha Karr, PharmD, BCPS
Assistant Professor
Midwestern University
College of Pharmacy-Glendale
Learning Objectives

Upon conclusion of this CPE activity, the participant should be able to...

- describe patient populations at high risk for venous thromboembolism (VTE)
- discuss evidence-based options for prophylaxis against VTE

Venous Thromboembolism (VTE): What is it?
VTE Pathophysiology

- VTE is a terminology that can be used for deep venous thrombosis (DVT) or pulmonary embolism (PE)
- Thrombi, or clots, can develop in the lower extremity vasculature when venous stasis or other high risk conditions exist
- The thrombus or thrombi can become disrupted, break away from the vessel wall, and travel to the lungs (pulmonary embolism, or PE)

VTE pathophysiology

**Virchow’s Triad**

**Inherited:**
- Antithrombin III deficiency
- Factor V Leiden mutation/activated Protein C resistance
- ↑ Factor VIII activity
- Hyperhomocysteinemia
- Protein C or S deficiency
- Prothrombin gene mutation

**Acquired:**
- Active cancer
- Antiphospholipid Syndrome
- Estrogen use
- Heparin-induced thrombocytopenia
- Hyperhomocysteinemia
- Pregnancy

- Prior thrombus
- Sepsis
- Spinal cord injury
- Surgery
- Trauma
- Vasculitis
- Venous Access

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**Venous Thromboembolism**

Why do we care? It’s a national epidemic!
U.S. Statistics

- Over 1 million DVT events
- More than 100,000 deaths from PE
- Costs to society:
  - About 1.5 billion in 2002
  - Prolongs hospital length of stay
  - Second leading cause of medical complications
  - Third leading cause of preventable mortality
  - Significant cause of excessive hospital charges

VTE-associated morbidity and mortality

- High incidence of postthrombotic syndrome
- Risk of VTE recurrence at 10 years: up to 30%
- Survival after 90 days:
  - for DVT, about 92%
  - can be as low as 52% for PE
- Survival after 8 years:
  - about 65% for DVT
  - as low as 35% for PE
VTE: Who is at most risk?

DVT Risk in Hospitalized Patients

<table>
<thead>
<tr>
<th>LEVEL</th>
<th>Examples</th>
<th>Risk (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LOW</td>
<td>• Minor surgery in mobile patients (including laparoscopic)</td>
<td>&lt;10%*</td>
</tr>
<tr>
<td></td>
<td>• Ambulatory medical patients</td>
<td></td>
</tr>
<tr>
<td>MODERATE</td>
<td>• Surgery</td>
<td>10-40%*</td>
</tr>
<tr>
<td></td>
<td>⊕ General surgery</td>
<td></td>
</tr>
<tr>
<td></td>
<td>⊕ Open gynecologic surgery</td>
<td></td>
</tr>
<tr>
<td></td>
<td>⊕ Urologic surgery</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Medical patients: bed rest or “sick”</td>
<td></td>
</tr>
<tr>
<td>HIGH</td>
<td>• Hip or knee arthroplasty, hip fracture surgery</td>
<td>40-80%*</td>
</tr>
<tr>
<td></td>
<td>• Major trauma, spinal cord injury</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• High VTE risk + high bleeding risk</td>
<td></td>
</tr>
</tbody>
</table>

*DVT risk without prophylaxis

Adapted from: Geerts WH, et al. CHEST 2008; 133:451S-453S.
VTE: A preventable disease state!!

If we can prevent VTE, why such a high incidence??

- Failure to provide prophylaxis
- Limited compliance with guidelines
  - Fear of increased risk bleeding
  - Lack of physician time
  - Lack of nursing and other healthcare staff
  - Lack of guideline knowledge or confusion
  - Lack of education across disciplines
  - System failures
  - Others

Exactly who is getting prophylaxis? According to ENDORSE, not many!

**ENDORSE: VTE risk/prophylaxis in acute care**

- Epidemiologic International Day for the Evaluation of Patients at Risk for Venous Thromboembolism in the Acute Hospital Care Setting study
- Multinational cross-sectional study using retrospective chart review
  - 358 hospitals, 32 countries
- **Objectives:**
  - to assess the prevalence of VTE risk in the acute hospital care setting
  - determine the % at risk patients receiving appropriate VTE prophylaxis
- **Patient population:**
  - all patients ≥ age 40 admitted to a medical ward (55%)
  - all patients ≥ age 18 admitted to surgical ward (45%)
- **Results:**
  - Patients found to be at risk for VTE (per ACCP criteria) 51.8%
  - Those receiving VTE prophylaxis as per guidelines (CHEST 2004):
    - At risk medical patients: 39.5%
    - At risk surgical patients: 58.5%

Recent VTE Initiatives

- The Joint Commission
  - VTE core measures set—six components required for hospitals to meet accreditation requirements
  - Includes VTE prophylaxis within 24 hrs of admission to hospital or ICU

- Surgical Care Improvement Project (SCIP)
  - A national partnership of organizations (including Joint Commission) to improve surgical care, reduce complications
  - Requires documentation of VTE prophylaxis administered within 24 hrs of surgery

- Others promoting the importance of VTE prophylaxis:
  - Health Services Advisory Group Resource Center
  - Institute for Healthcare Improvement (IHI)
  - U.S. Surgeon General’s Call to Action
What else should we be doing?

VTE Prevention Initiatives at the local/institution level

- Hospital Protocols promoting VTE prophylaxis
- Electronic Medical Record alerts: prompts for prescribing of VTE prophylaxis
- Hospital admission order sets with defaults to give VTE prophylaxis; option to opt out
- Risk assessment models
- Computer reports generated by inpatient pharmacies to identify and intervene in cases of no prophylaxis
VTE Prevention:
Evidence-based recommendations

### American College of Chest Physicians (ACCP) 2008

<table>
<thead>
<tr>
<th>Risk Level</th>
<th>Suggested Thromboprophylaxis Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>LOW</td>
<td>• No specific prophylaxis</td>
</tr>
<tr>
<td></td>
<td>• Early and aggressive ambulation</td>
</tr>
<tr>
<td>MODERATE</td>
<td>• Low Molecular Weight Heparin (LMWH)</td>
</tr>
<tr>
<td></td>
<td>• Low Dose Unfractionated Heparin (LDUH) with BID-TID dosing</td>
</tr>
<tr>
<td></td>
<td>• Fondaparinux</td>
</tr>
<tr>
<td></td>
<td>• Mechanical thromboprophylaxis*</td>
</tr>
<tr>
<td>HIGH</td>
<td>• LMWH</td>
</tr>
<tr>
<td></td>
<td>• Fondaparinux</td>
</tr>
<tr>
<td></td>
<td>• Oral Vitamin K antagonist (VKA; i.e. warfarin)</td>
</tr>
</tbody>
</table>

*Mechanical thromboprophylaxis with IPC, VFP, or GCS as an adjunct to anticoagulant-based prophylaxis or as a substitute only when bleeding risk outweighs VTE risk

Adapted from: Geerts WH, et al. CHEST 2008; 133:451S-453S.
VTE prevention:
ACCP 2008 specific recommendations

<table>
<thead>
<tr>
<th>Type of Patient</th>
<th>Prophylaxis (Grade)</th>
<th>Duration (Grade)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical w/heart failure or resp. disease OR confined to bed and ≥1 risk factor for VTE</td>
<td>LMWH (1A) LDHU (1A) Fondaparinux (1A)</td>
<td>7-14 days based on MEDENOX, PREVENT, and ARTEMIS studies</td>
</tr>
<tr>
<td>General Surgery: Mod. Risk</td>
<td>LMWH (1A) LDHU (1A) Fondaparinux (1A)</td>
<td>Until ambulating/hospital discharge (1A)</td>
</tr>
<tr>
<td>General Surgery: Higher Risk</td>
<td>LMWH (1A) LDHU 3x/day (1A) Fondaparinux (1A)</td>
<td>Until hospital discharge (1A) Consider extended prophylaxis up to 28 days post-discharge (1A)</td>
</tr>
<tr>
<td>Bariatric Surgery</td>
<td>LMWH (1C) LDHU 3x/day (1C) Fondaparinux (1C)</td>
<td>??Until hospital discharge?</td>
</tr>
<tr>
<td>Total Hip Replacement (THR)</td>
<td>LMWH VKA fondaparinux</td>
<td>At least 10 days (1A for all) 10-35 days with LMWH (1A) 10-35 days with VKA (1B) 10-35 days with fondaparinux (1C)</td>
</tr>
<tr>
<td>Total Knee Replacement (TKR)</td>
<td>LMWH VKA fondaparinux</td>
<td>At least 10 days (1A for all) 10-35 days (1C for all)</td>
</tr>
<tr>
<td>Hip Fracture Surgery</td>
<td>LMWH VKA Fondaparinux</td>
<td>At least 10 days (1A for all) 10-35 days with fondaparinux (1A) 10-35 days with VKA or LMWH (1C)</td>
</tr>
</tbody>
</table>

Adapted from: Geerts WH, et al. CHEST 2008; 133:381S-453S.

VTE prevention:
prophylactic doses of anticoagulants

<table>
<thead>
<tr>
<th>Anticoagulant</th>
<th>Notes:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>DO NOT USE! ACCP 2008 guidelines STRONGLY recommend against use of aspirin ALONE as thromboprophylaxis against VTE for any patient group (1A)!!</td>
</tr>
<tr>
<td>Enoxaparin</td>
<td>40 mg SUBQ once daily (acutely ill patients) 40 mg SUBQ once daily (abdominal surgery)** 30 mg SUBQ every 12 hours (TKR)** 30 mg SUBQ every 12 hours (THR)** - anti-factor Xa monitoring recommended for renal impairment or obesity - ↑ dose to 30 mg once daily in renal impairment - ↑ dose to 30-40 mg SC every 12 hours for abdominal or bariatric surgery in obese - consider reducing dose or monitoring anti-factor Xa for body weight &lt;45 kg</td>
</tr>
<tr>
<td>Dalteparin</td>
<td>5000 international units SUBQ once daily (acutely ill patients) 25000 international units SUBQ once daily (abdominal surgery w/high dose for higher risk)** 5000 international units SUBQ once daily (THR)** - No specific dosage adjustments recommended for VTE prophylaxis; should adjust based on anti-factor Xa levels - Obesity adjustment is generally 7500 international units SC once daily</td>
</tr>
<tr>
<td>Fondaparinux</td>
<td>2.5 mg SUBQ once daily (ortho or abd. surgery) - DO NOT USE in renal failure (&lt;30 mL/min)</td>
</tr>
<tr>
<td>VKA</td>
<td>2.5 mg x 1 then adjust based on INR (ortho surgeries) - INR target of 2.5 (range 2.0-3.0)</td>
</tr>
<tr>
<td>LDHU</td>
<td>5000 units SUBQ every 8-12 hours (major surgery)</td>
</tr>
</tbody>
</table>

*Dosing regimens listed for reference only—consult individual institution protocols; **also given 1-2 hrs prior to surgery in most cases
VTE prevention: summary

- VTE is associated with significant morbidity and mortality
- VTE is often preventable
- VTE is not just an “inpatient” disease
- Many organizations are focusing efforts on increasing VTE awareness and prophylaxis
- Best protocols employ multidisciplinary teams
- Be familiar with groups at high risk for VTE
- Most hospitalized patients need VTE prophylaxis!
- Use evidence-based recommendations

Contact info: skarrx@midwestern.edu