Update on HIT Syndrome
Recent Advances in Management

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VTE meeting/in Casablanca
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No disclosure
Heparin-induced Thrombocytopenia

- Heparin-induced thrombocytopenia (HIT)
  - Considered a rarity in the past
    - Unrecognized by many clinicians
    - Diagnoses can be difficult to confirm
  - There was no therapeutic options other than discontinuation of heparin in the past
Why Hit is Important
Thrombocytopenia is one of the most common laboratory abnormalities found among hospitalized patients.
• The chance of significant exposure to heparin exceeds 50% in hospitalized patients.

  – Acute coronary syndrome
  – Pulmonary embolism
  – Deep venous thrombosis and prophylaxis
  – Stroke / atrial fibrillation
  – Heparinized pulmonary wedge catheters
  – Heparin flush
Fourteen-Year Study of HIT: Group II Results After Heparin Discontinuation

Cumulative Thrombotic Event Rate (%)

Days After Isolated HIT Recognized

52.8%

Thrombosis

- Thromboembolic complications
  - Occurs in 30% to 40% of HIT cases
  - Mortality estimated at 30%

Circulation 1999;100:587-93
Thromb Haemost 1993;70:554-61
Thrombosis

- Thrombosis is mostly venous more frequent than arterial, may result in
  - Bilateral deep venous thrombosis of the legs
  - Pulmonary embolism
  - Venous gangrene of fingers, toes, penis, or nipples
  - Myocardial infarction, stroke
  - Mesenteric arterial thrombosis
  - Limb ischemia and amputation

Circulation 1999;100:587-93
Thromb Haemost 1993;70:554-61
Lepirudin (recombinant hirudin)

- It is a thrombin inhibitor
- Approved in 1998 for anticoagulation in patients with heparin-induced thrombocytopenia (HIT) and thromboembolic disease
- In order to prevent further thromboembolic complications

What more ABOUT HIT?
What more to understand HIT?

- Definition
- Pathogenesis
- Clinical features
- How Diagnosis
- How to manage it? Especially in pregnancy, renal dialysis
- Update, ACCP Guidelines Recommendations.
- Could we prevent it?

- References
Definition

- Heparin-induced thrombocytopenia (HIT), also known as the ‘white clot syndrome’,

HIT is recognized as a clinicopathologic syndrome

- It is an antibody-mediated drug reaction
- characterized by:
  - Thrombocytopenia
  - Devastating thromboembolic complications,

  (including pulmonary embolism, ischemic limb necrosis necessitating limb amputation, acute myocardial infarction, and stroke)
HIT continue

M:F 1:2

- Though the exact incidence of HIT has not been well established,

- HIT has been noted to develop in up to 3–5% of patients exposed to heparin (UFH).

- Early reports that cited an incidence as high as 30% lacked a clear definition of thrombocytopenia and failed to differentiate HIT from non-immunemediated

- **Thrombosis 17% to 55% in untreated patients**
Pathogenesis
Cascade of events leading to formation of HIT antibodies and prothrombotic components
Type of HIT
HIT Syndrome

• Type I
  – associated with an early (within 4 days) and usually mild decrease in platelet count (rarely <100 x 10^9/L)
  – typically recovers within 3 days despite continued use of heparin
  – nonimmunologic mechanisms (mild direct platelet activation by heparin)
  – not associated with any major clinical sequelae
  – occurs primarily with high dose iv heparin
HIT Syndrome

• Type II
  – substantial fall in platelet count (30-50%)
  – count in the 50,000 - 80,000 /mm range
  – typical onset of 4-14 days
  – occurs with any dose by any route
  – induced by immunologic mechanisms
  – rarely causes bleeding (think of alternative Dx)
  – potential for development of life-threatening thromboembolic complications
Clinical features suggesting heparin induced thrombocytopenia

- HIT usually develops between 5 - 14 days after the commencement of heparin therapy and produces a variable but often profound degree of thrombocytopenia.

- 30% -50% decrease in platelet count from baseline while receiving heparin therapy

- A platelet count fall that begins prior to day 5 or in 24 hr (fast drop) is due to previous exposure to heparin or subacute
Clinical features suggesting heparin induced thrombocytopenia type II.

• Decrease in platelet count and associated thrombotic event while receiving heparin

• Heparin-associated skin necrosis, at the site of injection
Risk Factor of HIT

- Type of heparin
- Duration
- Gender
- Patient population
<table>
<thead>
<tr>
<th>Patient Population (Minimum of 4-d Exposure)</th>
<th>Incidence of HIT, %</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Postoperative patients</strong></td>
<td></td>
</tr>
<tr>
<td>Heparin, prophylactic dose</td>
<td>1–5</td>
</tr>
<tr>
<td>Heparin, therapeutic dose</td>
<td>1–5</td>
</tr>
<tr>
<td>Heparin, flushes</td>
<td>0.1–1</td>
</tr>
<tr>
<td>LMWH, prophylactic or therapeutic dose</td>
<td>0.1–1</td>
</tr>
<tr>
<td>Cardiac surgery patients</td>
<td><strong>1–3</strong></td>
</tr>
<tr>
<td><strong>Medical</strong></td>
<td></td>
</tr>
<tr>
<td>Patients with cancer</td>
<td>1</td>
</tr>
<tr>
<td>Heparin, prophylactic or therapeutic dose</td>
<td>0.1–1</td>
</tr>
<tr>
<td>LMWH, prophylactic or therapeutic dose</td>
<td>0.6</td>
</tr>
<tr>
<td>Intensive care patients</td>
<td>0.4</td>
</tr>
<tr>
<td>Heparin, flushes</td>
<td>&lt; 0.1</td>
</tr>
<tr>
<td>Obstetrics patients</td>
<td>&lt; 0.1</td>
</tr>
<tr>
<td>Risk for Developing HIT</td>
<td>Risk Factor</td>
</tr>
<tr>
<td>-------------------------</td>
<td>------------</td>
</tr>
<tr>
<td>High (&gt;1%)</td>
<td>• Postoperative or trauma patients, especially cardiac, vascular, or orthopedic surgery receiving UFH</td>
</tr>
<tr>
<td>Intermediate (0.1–1%)</td>
<td>• Postoperative patients receiving UFH flushes</td>
</tr>
<tr>
<td></td>
<td>• Postoperative patients receiving LMWH</td>
</tr>
<tr>
<td></td>
<td>• Medical or obstetrical patients treated with therapeutic or prophylactic doses of UFH</td>
</tr>
<tr>
<td>Low (&lt;0.1%)</td>
<td>• Medical or obstetrical patients treated with LMWH</td>
</tr>
</tbody>
</table>

UFH, unfractionated heparin; LMWH, low molecular weight heparin.
Clinical Features

- Thrombocytopenia is the most common clinical manifestation of HIT and occurs in 85% to 90% of patients. The characteristic onset of the platelet count fall in HIT is 5 to 10 days after initiation of heparin.

  Occasionally, thrombocytopenia can occur as long as 3 weeks after cessation of heparin (delayed-onset HIT).

- Although thrombocytopenia is the most common presenting feature of HIT, in up to 25% of patients with HIT the development of thrombosis precedes the development of thrombocytopenia.
VTE Accident
HIT Accident
Two Challenges

- Diagnosis
- Management
Diagnosis

Diagnosis is based on the combination of

- **Compatible clinical picture** (28)
- Thrombocytopenia <150,000 or 30-50 % drop in from the base line during heparin therapy
- **Diagnosis/thrombocytopenia**
- The presence of platelet-activating anti-pf4 antibodies
Clinical picture Assessment

- Clinical assessment plays an essential role in the diagnosis of HIT for two reasons:
  1. there is commonly a delay before the results of laboratory testing for HIT are available,
  2. isolated HIT antibodies are both frequent and not diagnostic of HIT.
Diagnosis

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- **Compatible clinical picture (28)**
- Thrombocytopenia <150,000 or 30-50% drop in from the base line during heparin therapy
- Diagnosis/thrombocytopenia
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ACCP-2012
Diagnosis/thrombocytopenia

• Absence of another cause for thrombocytopenia
  Differential Diagnosis of Acquired Thrombocytopenia
• The timing of thrombocytopenia
• The degree of thrombocytopenia

• Diagsoes
Differential Diagnosis of Acquired Thrombocytopenia

- **Drugs**
  - heparin
  - procainamide
  - diuretics (furosemide)
  - H$_2$ blockers (cimetidine)
  - thrombolytic therapy
  - GP IIb/IIIa antagonists

- **Devices**
  - membrane oxygenator
  - intra-aortic balloon pump

- **Pseudothrombocytopenia**
  - platelet clumping
  - hemodilution

- **Associated disorders**
  - hypersplenism
  - infections/sepsis
  - hypotension and subsequent disseminated intravascular coagulation

- **Other causes**
  - chronic idiopathic thrombocytopenia purpura with exacerbation
  - antiphospholipid antibody syndrome

Diagnosis of HIT
Diagnosis/thrombocytopenia

- Absence of another cause for thrombocytopenia
- The timing of thrombocytopenia
- The degree of thrombocytopenia
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Diagnosis/thrombocytopenia

- Absence of another cause for thrombocytopenia
- The timing of thrombocytopenia
- The degree of thrombocytopenia

Differential Diagnosis of Acquired Thrombocytopenia

Diagsoes
Diagnosis of HIT continue

• Onset of thrombocytopenia typically 5–14 days after initiation of heparin therapy but can occur earlier

• Occurrence of thromboembolic complications during heparin therapy

• \textbf{Diagnosis}
Differential Diagnosis of Acquired Thrombocytopenia

- **Drugs**
  - heparin
  - procainamide
  - diuretics (furosemide)
  - $H_2$ blockers (cimetidine)
  - thrombolytic therapy
  - GP IIb/IIIa antagonists

- **Devices**
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  - chronic idiopathic thrombocytopenia purpura with exacerbation
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Clinical picture Assessment

Clinical assessment plays an essential role in the diagnosis of HIT for two reasons:

1. There is commonly a delay before the results of laboratory testing for HIT are available,
2. Management decisions must be made immediately.
3. Isolated HIT antibodies are both frequent and not diagnostic of HIT.
Serological test

Serologically Proven HIT occurs in 1.5% to 3% of patients with heparin exposure
The currently available in vitro diagnostic assays for HIT are either

1. **Immunoassays or antigen assays** that detect the presence of HIT antibodies, and

2. **Functional assays** that detect evidence of platelet activation
# Common Laboratory Tests for HIT

<table>
<thead>
<tr>
<th>Test</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAA</td>
<td>Rapid and simple</td>
<td>Low sensitivity - not suitable for testing multiple samples</td>
</tr>
<tr>
<td>SRA</td>
<td>Sensitivity &gt;90%</td>
<td>Washed platelet (technically demanding), needs radiolabeled material $^{14}$C</td>
</tr>
<tr>
<td>HIPA</td>
<td>Rapid, sensitivity &gt;90%</td>
<td>Washed platelets</td>
</tr>
<tr>
<td><strong>ELISA</strong></td>
<td>High sensitivity, detects IgA and IgM</td>
<td><strong>High cost</strong>, lower specificity for clinically significant HIT</td>
</tr>
</tbody>
</table>
Commercial antigen assay

- Two antigène assays:
  - ID-PaGIA Heparin/PF4 antibody test (DiaMed),
  - GTI-PF4 (Genetics Testing Institute [GTI])
Antigen Assay

two antigen assays: GTI-PF4 (Genetics Testing Institute [GTI]) and ID-PaGIA Heparin/PF4 antibody test (DiaMed AG)
HIT-associated thrombosis

- HIT is prothrombotic
  - 18% without HIT developed thrombosis
  - 89% with HIT developed thrombosis
Thrombosis

Thrombosis is mostly venous than arterial may result in

- Deep vein thrombosis *
- Pulmonary embolism *
- Venous limb gangrene
- Adrenal hemorrhagic infarction
- Cerebral sinus thrombosis

Venous thrombotic events predominate over arterial events by 4:1 ratio. Usually involving large vessels.

Circulation 1999;100:587-93
Thromb Haemost 1993;70:554-61
## Pretest Scoring System for HIT: The 4 T’s

<table>
<thead>
<tr>
<th>4T’s</th>
<th>2 points</th>
<th>1 point</th>
<th>0 point</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombocytopenia</td>
<td>Platelet count fall &gt;50% and platelet nadir ≥20*</td>
<td>Platelet count fall 30-50% or platelet nadir 10-19</td>
<td>Platelet count fall &lt;30% or platelet nadir &lt;10</td>
</tr>
<tr>
<td>Timing of platelet count fall</td>
<td>Clear onset between days 5-10 or platelet fall ≤1 day (prior heparin exposure within 30 days)</td>
<td>Consistent with days 5-10 fall, but not clear (e.g. missing platelet counts); onset after day 10⁺; or fall ≤1 day (prior heparin exposure 30 100 days ago)</td>
<td></td>
</tr>
<tr>
<td>Thrombosis or other sequelae</td>
<td>New thrombosis (confirmed); skin necrosis; acute systemic reaction postintravenous unfractionated heparin (UFH) bolus</td>
<td>Progressive or recurrent thrombosis; Non-necrotizing (erythematous) skin lesions; Suspected thrombosis (not proven)</td>
<td></td>
</tr>
<tr>
<td>Other causes for thrombocytopenia</td>
<td>None apparent</td>
<td>Possible</td>
<td>Definite</td>
</tr>
</tbody>
</table>
4Ts - Scoring system

- 0-3: low probability
- 4-5: intermediate
- 6-8: high
Management Of HIT
Goals for management

• The goals of management of HIT are to reduce the thrombotic risk by reducing platelet activation and thrombin generation.
Treatment of Suspected HIT

- Discontinue all heparin immediately, including
  - Heparin flushes
  - Heparin-coated pulmonary catheters
  - Heparinized dialysate and any other medications or devices containing heparin

- Confirm diagnosis of HIT with the appropriate laboratory test
- Consider alternative anticoagulation
- Monitor carefully for thrombosis
- Monitor platelet counts until recovery
- Avoid prophylactic platelet transfusions
Management

- Warfarin monotherapy in active heparin induced thrombocytopenia is also contraindicated, Skin Necrosis

ACCP Guldilne2012

*Ann Intern Med* - 1-NOV-1997; 127(9): 804-12
Skin Necrosis in HIT

venous Limb Gangrene
(with use of warfarin in HIT)

Venous Limb Gangrene (with use of warfarin in HIT)

- Patients with acute heparin-induced thrombocytopenia and deep venous thrombosis who are treated with warfarin seem to be at risk for developing venous limb gangrene.

- Laboratory studies suggest that this syndrome is related to a warfarin-induced failure of the protein C anticoagulant pathway to regulate the increased thrombin generation that occurs in patients with heparin-induced thrombocytopenia.

- **Management**
Antithrombin Drugs

Agents that reduce or inhibit thrombin

- Lepirudin (refludan)
- Danaparoid sodium (orgaran)
- Argatroban (novastan)
## Treatment Options for HIT

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV Lepirudin</td>
<td>0.4 mg/kg load</td>
<td>preferred therapy, if available</td>
</tr>
<tr>
<td></td>
<td></td>
<td>adjust those for renal insufficiency</td>
</tr>
<tr>
<td></td>
<td></td>
<td>check aPTT 4hr after dose adjustment</td>
</tr>
<tr>
<td>IV Danaparoid</td>
<td>400 U/hr x 4 hr → 300 U/hr x 4hr → 100 - 370 U/hr</td>
<td>direct thrombin inhibitor cannot be used</td>
</tr>
<tr>
<td></td>
<td></td>
<td>monitor anti-factor Xa levels</td>
</tr>
<tr>
<td></td>
<td></td>
<td>adjust those for renal insufficiency</td>
</tr>
<tr>
<td>SC Danaparoid</td>
<td>750 U every 12 hr</td>
<td>may be used for low-risk cases</td>
</tr>
<tr>
<td></td>
<td></td>
<td>must have ability to monitor anti-factor Xa levels</td>
</tr>
<tr>
<td></td>
<td></td>
<td>if renal insufficiency is present</td>
</tr>
<tr>
<td>Warfarin</td>
<td></td>
<td>consider for long-term anticoagulation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Do not start warfarin without concurrent alternative anticoagulation</td>
</tr>
</tbody>
</table>

05/00  medslides.com 59
• **Recommendation**

  - In patients with confirmed HIT, we recommend that the VKA be overlapped with a nonheparin anticoagulant for a minimum of 5 days and until the INR is within the target range over shorter periods of overlap (Grade 1C).
Duration of Therapy in Patients With HITT or HIT

- For patients with HIT T, we suggest VKA therapy or an alternative anticoagulant to be continued for 3 months.

- For patients with HIT, we suggest VKA therapy or an alternative anticoagulant to be continued for 4 weeks.
Platelet transfusion in HIT?

- Spontaneous bleeding is uncommon with HIT despite sometimes profound thrombocytopenia.
- May exacerbate HIT?

There is no direct evidence supporting an increased risk of thrombosis in patients with HIT who are given platelet transfusions. However, the evidence is also too limited to support the safety of platelet transfusions.

ACCP - Recommendation
In patients with HIT and severe thrombocytopenia, we suggest giving platelet transfusions only if bleeding or during the performance of an invasive procedure with a high risk of bleeding (Grade 2C).
Renal insufficiency in HIT

- Both lepirudin and danaparoid are renally cleared, but argatroban is not.

- Furthermore, there are retrospective, observational data to suggest that the use of lepirudin in renal failure is associated with an increased risk of major bleeding,

- Whereas a Secondary Analysis of the argatroban historical controlled trials did not show such a relationship.

Recommendation:
In patients with HITT and renal insufficiency, we suggest the use of argatroban over other nonheparin anticoagulants (Grade 2C).
Patients Who Require Renal Replacement Therapy

- Recommendation

- In patients with acute HIT who require renal replacement therapy, we suggest the use of argatroban or danaparoid over other nonheparin anticoagulants (Grade 2C).
HIT during pregnancy

- The incidence of HIT during pregnancy is lower than in the non-pregnant population, especially when LMWH is used (at either prophylactic or therapeutic doses)

  one in 1,167 pregnancies.
  zero in 2,777 pregnancies

Recommendation
In pregnant patients with acute or subacute HIT, we suggest danaparoid over other nonheparin anticoagulants (Grade 2C).
We suggest the use of lepirudin or fondaparinux only if danaparoid is not available (Grade 2C).
Management of Patients With a Past History of HIT

• Because there are no clinical trials evaluating the safety of this premise, our recommendations are based on the incidence of recurrent HIT

• Patients with a past history of HIT can theoretically be re-exposed to heparin, because of several unique properties of HIT antibodies.

• First, the HIT antibody is known to be transient, with a median time to disappearance of 50 to 80 days (depending on the assay performed).

• Second, there is no evidence to suggest that patients with a prior history of HIT (who are c
Adjunctive Therapies for HIT

- **Plasmapheresis**
  - can reduce the concentration of HIT antibodies
  - replace deficient plasma anticoagulant factors

- **Aspirin/Clopidogril/Gp2b3a inhibitors**
  - can inhibit platelet activation by HIT antibodies
Steps to Prevent HIT

- LMWH preferred over UFH
- Oral anticoagulation should be started as early as possible to reduce the duration of heparin exposure
- Intravenous adapters should not be flush with heparin
- Monitoring serial plate counts during heparin therapy
- Porcine heparin preferred over bovine heparin
- Awareness of this condition and proper intervention
- Reduced the incidence of HIT COMPLECATION
Conclusions

• Heparin, although an important anticoagulant, has several drawbacks, most notably its ability to cause HIT
• HIT can lead to severe and even life-threatening thromboembolic disorders. Suspect and treat.
• Treatment of HIT should be initiated before laboratory confirmation
• A new generation of drugs such as the thrombin inhibitors can provide important new options for the treatment and possible prevention of HIT
Conclusion

• Is the days for heparin will be numbered

Thank you
References

1. 9th ACCP Guideline, Chest, Feb 2012
References

- Danaparoid (Orgaran) for the treatment of heparin-induced thrombocytopenia (HIT) and thrombosis. Warkentin TE. Blood. 1996;88(Suppl 1):626a
Antithrombotic Treatment

- **Warfarin**
  - caution if INR >4
  - high INR corresponds to a marked reduction in protein C levels, i.e., there is insufficient protein C activity to regulate the ↑thrombin generation found in HIT
  - associated with progression of deep venous thrombosis to venous limb gangrene
  - considered contraindicated in acute HIT, but reasonable to use in longer-term anticoagulation

Thromb Haemost 1998;79:1-7
Ann Intern Med 1997;127:804-812
Antithrombotic Treatment

• **LMWH (enoxaparin and dalteparin)**
  – in vitro studies showed virtually 100% cross-reactivity with HIT antibodies
  – lack large, controlled studies
  – anecdotal reports of persistent or recurrent thrombocytopenia during treatment
Lepirudin (Refludan®)

- The only direct thrombin inhibitor approved for use and for treatment of HIT in the U.S.
- German trial of 200 patients with HIT
  - 75% to 81% effectively anticoagulated
  - Significant reduction in composite endpoints (death, limb amputation, new thrombotic complications) compared with historical control
    - 7 day: 10% vs 23%
    - 35 day: 25% vs 52%

Blood 1996;88(suppl):281a
Danaparoid (Orgaran®)

- a low-molecular-weight heparinoid
  - mixture of anticoagulant glycosaminoglycans (heparin sulfate, dermatan sulfate, and chondroitin sulfate) with predominant anti-factor Xa activity
- rapid anticoagulant effect with IV bolus
- long half-life (~25 hours) for anti-Xa activity
- in vitro cross-reactivity with the HIT antibody (10% to 40%) does not predict development of thrombocytopenia or thrombosis

Blood 1996;88(Suppl 1):626a
Thromb Haemost 1993;70:554-561
Argatroban (Novastan®)

- a small synthetic non-polypeptide molecule
- a direct thrombin inhibitor
- FDA approved June 30, 2000
- has the same theoretical advantages of lepirudin
  - short half-life (< 1 hr)
  - lack of cross-reactivity for HIT antibodies
  - potent antithrombin activity
- metabolized predominantly by the liver, may require dose adjustment
- excreted normally even in severe renal failure
Lepirudin (Refludan®)

• A direct thrombin inhibitor
  – recombinant form of the leech anticoagulant hirudin, the most potent direct thrombin inhibitors yet identified
• Rapid anticoagulant effect with IV bolus
• Relatively short half-life (1.3 hours)
• Relatively contraindicated in renal failure
• Anticoagulant effect readily monitored with aPTT (target range 1.5-3.0 times normal)
# Do’s and Don’ts of HIT Management

<table>
<thead>
<tr>
<th>Drug</th>
<th>Do</th>
<th>Don’t</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin</td>
<td>x</td>
<td></td>
<td>warfarin in the absence of an anticoagulant can precipitate venous limb gangrene</td>
</tr>
<tr>
<td>Platelet</td>
<td>x</td>
<td></td>
<td>infusing platelets merely “adds fuel to the fire”</td>
</tr>
<tr>
<td>Vena caval filter</td>
<td>x</td>
<td></td>
<td>often results in devastating caval, pelvic, and lower leg venous thrombosis</td>
</tr>
<tr>
<td>LMWH</td>
<td>x</td>
<td></td>
<td>low molecular weight heparin usually cross-react with unfractionated heparin after HIT or HITTS (HIT thrombosis syndrome) has occurred</td>
</tr>
<tr>
<td>Ancrod</td>
<td>x</td>
<td></td>
<td>not readily available; difficult to titrate dose</td>
</tr>
<tr>
<td>Danaparoid</td>
<td>x</td>
<td></td>
<td>cross-reacts with UFH in about 10-15% of cases; titrate with unwieldy anti-factor Xa levels</td>
</tr>
<tr>
<td>Hirudin</td>
<td>x</td>
<td></td>
<td>Beware renal insufficiency, antibody formation</td>
</tr>
<tr>
<td>Plasmapheresis</td>
<td>x</td>
<td></td>
<td>removes micro-particles formed from platelet activation; not a standard indication</td>
</tr>
<tr>
<td>Argatroban</td>
<td>x</td>
<td></td>
<td>FDA approved June 30, 2000, monitor hepatic</td>
</tr>
</tbody>
</table>