Immune Thrombocytopenias

Andreas Greinacher

Institut für Immunologie und Transfusionsmedizin
Universität Greifswald, Germany
Disclosures for
Andreas Greinacher

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<table>
<thead>
<tr>
<th>Role</th>
<th>Disclosures</th>
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<tbody>
<tr>
<td>Research Support/P.I.</td>
<td>Boehringer-Ingelheim; Bayer Healthcare</td>
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<td>No relevant conflicts of interest to declare</td>
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<td>No relevant conflicts of interest to declare</td>
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<td>Speakers Bureau</td>
<td>No relevant conflicts of interest to declare</td>
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<td>Honoraria</td>
<td>Merck, Schering-Plough, Mitsubishi Pharma, GSK, Bayer</td>
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<td>Scientific Advisory Board</td>
<td>Boehringer-Ingelheim</td>
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</table>
Immune Thrombocytopenias

- Autoimmune-Thrombocytopenia
- Alloimmune-Thrombocytopenia
- Drug-Induced-Immune-Thrombocytopenia
  - drug induced autoimmune TP
  - drug dependent TP
  - GP IIb/IIIa inhibitor induced TP
  - heparin-induced TP
Definition of ITP

Primary immune thrombocytopenia

Platelet count <100,000/µL

No other cause of thrombocytopenia

No clinically evident secondary form

Secondary ITP: SLE, CLL, HIV, Hepatitis C

Rodeghiero et al. Blood (2009); 113:2386
Provan et al. Blood (2010); 115: 168
Phases of the Disease

- **Newly-diagnosed ITP**: within three months from diagnosis
- **Persistent ITP**: between 3 to 12 months from diagnosis
- **Chronic ITP**: lasting for more than 12 months
Clinical Symptoms in ITP
Demographics of ITP

circa 1960


circa 2010

Pathophysiology of ITP in 2002

New concept:
in part ITP is also caused by impaired platelet production
Plasma TPO levels in ITP


Suppression of megakaryocyte production by ITP plasma

Megakaryocyte Ultrastructure

normal

(para)apoptosis

T-cell mediated platelet cytotoxicity

- Platelet antibodies not detected in ~1/3 patients
- Impaired thrombopoiesis

Recognition of desialylated platelets by the Ashwell receptor

Clearance of desialylated platelets by the Ashwell receptor

Protection against disseminated intravascular coagulation

Cornelis van 't Veer & Tom van der Poll
Refrigeration up-regulates glycosidases to the surface of platelets.

The mechanism by which AAbs in ITP patients lead to platelet clearance differ between individuals.
Deglycosylation of human autoantibodies (AAb)

AAb (IgG) → de-AAb (IgG)

AAbs → de-AAbs

Asn297

Galactose, Mannose, GlcNAc, Fucose, StaticAcid

AAbs

de-AAbs

Ponceau S (Protein)

LCA (N-Glycan)

50 kDa

47 kDa

25 kDa

cell number

antibody binding to platelets (FITC)

ctl  AAbs  ctl  de-AAbs
AAb-mediated phagocytosis

- Green: platelets (CMFDA)
- Red: monocyte membrane (CD14)
- Blue: nucleus (Hoechst 33342)

**Comparison:**

- Control IgG
- AAb
- de-AAb

**Graph:**

- Phagocytic activity %
- Control, non-ITP, AAbs, de-AAbs
- p < 0.001
- p < 0.001
Platelet destruction in NOD/SCID mice

1. Introduction of human PRP into the retroorbital plexus

2. Intraperitoneal injection of antibodies of interest

3. Periodical collection of blood samples

4. Flow analysis (number, function)

Boylan B et al, Blood 2006; Bakchoul T et al, Blood 2013
Survival of human platelets

in the absence or presence of complement

control IgG
(n = 4)

non complement-activating AAb
(n = 8)

complement-activating AAb
(n = 7)

\[ p = 0.27 \]

\[ p = 0.003 \]
Origination of ITP

- Hereditabilty
- Infection
  - Molecular mimicry
    (- Epitope spread)
Heritability of ITP

If more than 1 family member has chronic thrombocytopenia
hereditary platelet disorders are most likely!!
MYH-9, GATA-1, von Willebrand type IIB
Bernard Soulier syndrome

Greifswald experience:
90 patients with MYH-9 disorder
5 patients with BSS
4 patients with vWD Type IIB
1 family with ITP

Estimated prevalence of 2° ITP in US

Cines et al. Blood 2009;113:6511
SECONDARY IMMUNE THROMBOCYTOPENIA

- Autoimmune:
  - Lupus (SLE)
  - Antiphospholipid antibody syndrome (APLS)
  - Immune Thyroid Disease
  - Evan’s Syndrome

- Lymphoproliferative:
  - CLL & WDLL
  - Hodgkin’s
  - LGL

- Infectious
Immune thrombocytopenia post-infection

HIV  HCV  H.pylori
HOW CAN AN INFECTIOUS AGENT INDUCE THROMBOCYTOPENIA?

- **Infection of megakaryocytes:**
  Decreased production or platelets by infected megakaryocytes.

- **Immune complex disease:**
  Immune complexes binding to platelet FcR and then secondary clearance by macrophages.

- **Immune dysregulation:**
  Loss of recognition of self with the development of anti-platelet antibodies.

- **Antigenic mimicry:**
  Antibodies against antigens of the infectious agent cross-react with platelet epitopes.
Immune thrombocytopenia post-infection: Molecular mimicry GP IIIa (aa 49-66)

Nardi. M. et al. PNAS (1997);94:7589

HIV

Platelet

HCV

Zhang et al. Blood (2009);113:4086

H. pylori

Cag A

Takahasi, T. et al. Br H Haem (2004);124:91
THROMBOCYTOPEINA WITH CHRONIC HEPATITIS C

• Thrombocytopenia (< 150 x 10⁹/L):
  151 of 368 (41%) patients with chronic HCV
  - 10 of 53 (19%) with chronic HBV.

• Thrombocytopenia (< 50 x 10⁹/L): 9% of HCV infected patients

Nagamine et al. J Hepatol 1996; 24: 135
Characteristics of HCV(+) vs. HCV(-) ITP

- Older and equally distributed between the sexes
- Bleeding at higher platelet counts
- Corticosteroids are less effective than in non-HCV ITP and may increase viral reproduction
- ITP may respond to IFNγ.

**RESPONSE TO TREATMENT**  
**HCV+ vs. HCV- ITP**

<table>
<thead>
<tr>
<th>TREATMENT MODALITY</th>
<th>HCV+ N (%)</th>
<th>HCV- N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corticosteroids</td>
<td>9/33 (20.7%)</td>
<td>145/266 (50.4%)</td>
</tr>
<tr>
<td>Immunoglobulin Anti-Rh D</td>
<td>8/9 (90%)</td>
<td>10/118 (90%)</td>
</tr>
<tr>
<td>Splenectomy</td>
<td>7/12 (58%)</td>
<td>42/65 (65%)</td>
</tr>
<tr>
<td>Interferon alpha</td>
<td>16/22 (73%)</td>
<td>0</td>
</tr>
</tbody>
</table>

IFN treatment causes thrombocytopenia. Low platelet count is a frequent cause to stop IFN treatment of HCV infection prematurely.

Phase II Study of Eltrombopag in Hepatitis C Thrombocytopenia

Heterogeneity in ITP response to eradication of *H. pylori*


Pooled Response Rate = 50.3% (41.6% to 59.0%)
SECONDARY IMMUNE THROMBOCYTOPENIA

- Autoimmune:
  - Lupus (SLE)
  - Antiphospholipid antibody syndrome (APLS)
  - Immune Thyroid Disease
  - Evan’s Syndrome

- Lymphoproliferative:
  - CLL & WDLL
  - Hodgkin’s
  - LGL

- Infectious:
  - HIV
  - HCV
  - H. pylori
# Antinuclear antibodies in ITP

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>n</th>
<th>(+)ANA</th>
<th>SLE</th>
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<tr>
<td>Perez</td>
<td>1985</td>
<td>18</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Anderson</td>
<td>1985</td>
<td>117</td>
<td>24</td>
<td>5</td>
</tr>
<tr>
<td>Panzer</td>
<td>1989</td>
<td>45</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Kurata</td>
<td>1994</td>
<td>66</td>
<td>29</td>
<td>0</td>
</tr>
<tr>
<td>Leung</td>
<td>2001</td>
<td>220</td>
<td>76</td>
<td>3</td>
</tr>
<tr>
<td>Li</td>
<td>2005</td>
<td>545</td>
<td>39</td>
<td>3/2*</td>
</tr>
<tr>
<td>Altinas</td>
<td>2007</td>
<td>108</td>
<td>36</td>
<td>1*</td>
</tr>
<tr>
<td>Abbasi</td>
<td>2007</td>
<td>41</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td>1160</td>
<td>227</td>
<td>16</td>
</tr>
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</table>

227 (20%)  
16 (1.4%)
## Incidence of APLA in ITP

<table>
<thead>
<tr>
<th>Author</th>
<th>Journal</th>
<th>Incidence</th>
<th>APLA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nomura</td>
<td>Ann Hematol ‘94</td>
<td>13/56 (23%)</td>
<td>CL</td>
</tr>
<tr>
<td>Stasi</td>
<td>Blood, ‘94</td>
<td>69/149 (46%)</td>
<td>CL, LA</td>
</tr>
<tr>
<td>Arfors</td>
<td>Eur J Hematol ‘96</td>
<td>12/30 (30%)</td>
<td>CL</td>
</tr>
<tr>
<td>Lipp</td>
<td>Eur J Hematol ‘96</td>
<td>52/71 (70%)</td>
<td>CL, PS</td>
</tr>
<tr>
<td>Sung</td>
<td>Plts ‘99</td>
<td>6/57 (11%)</td>
<td>b2GPI</td>
</tr>
<tr>
<td>Diz</td>
<td>Blood. ‘01</td>
<td>31/82 (38%)</td>
<td>CL, LA</td>
</tr>
<tr>
<td>Bidot</td>
<td>Br J Haem ‘04</td>
<td>26/40 (66%)</td>
<td>multiple</td>
</tr>
</tbody>
</table>

**Total** 196/485 (43.1%)
Prevalence of APLA, ANA, ATA in ITP

- ANA: 15-25%
- APLA: 30-40%
- ATA: 25-50%
- DAT: 1-5%

ITP

Another autoantibody
## Thrombosis in ITP with APLA

<table>
<thead>
<tr>
<th>Study</th>
<th>APLA (+)</th>
<th>APLA (-)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fanauchi ‘97</td>
<td>5/7 (71%)</td>
<td>3/20 (15%)</td>
</tr>
<tr>
<td>Diz-Kuckkaya ‘01</td>
<td>14/31 (45%)</td>
<td>3/51 (2.3%)</td>
</tr>
<tr>
<td>Bidot ‘04</td>
<td>8/19 (42%)</td>
<td>-----</td>
</tr>
<tr>
<td>Pierrot-Deseilligny ‘08</td>
<td>4/55 (7%)</td>
<td>10/160 (6%)</td>
</tr>
</tbody>
</table>
### Treatment of ITP: When? Why? How?

<table>
<thead>
<tr>
<th>platelets</th>
<th>spleen/RES</th>
<th>Immune system</th>
</tr>
</thead>
</table>
| - Platelet transfusion  
- TPO-receptor agonists | - i.v. IgG  
(2g/kg bw over 2 or 4 days)  
- anti-D  
- splenectomy | - steroids  
- anti-CD20  
(375 mg/m²/week, over 4 weeks) |

- [Image of platelets and spleen/RES]
- [Image of immune system components (T and B cells)]
- [Diagram of immune system function]
## Treatment

<table>
<thead>
<tr>
<th>Platelets</th>
<th>20,000-30,000</th>
<th>30,000-50,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>No symptoms</td>
<td>(treatment)</td>
<td>wait and watch</td>
</tr>
<tr>
<td>Petechiae or ecchymoses</td>
<td>treatment</td>
<td>treatment</td>
</tr>
<tr>
<td>Bleeding</td>
<td>treatment</td>
<td>treatment</td>
</tr>
</tbody>
</table>

- Prednisone 1-2 mg/kg/d (4-6 W) or high dose-dexamethasone (oral 40 mg/day for 4 days)

- ivIgG 0.4 g/kg/d for 1-5 days

- Anti-D i.v./s.c.

Rodeghiero et al. Blood, 2009
Definite Indication for Treatment

wet purpura
Life threatening bleeding
- Platelet concentrates
- rFVIIa (25 µg/kg bw)

Severe bleeding
- 100 mg prednisolone per day or
- high dose-dexamethasone (40 mg/d for 4d)

- combined with 2 g/kg b.w. ivIG (over 2 or 4d)
Patient

• 46 year old man.
• 10 year history of ITP: platelet count 20-40,000/µL; no major bleeding.
• wait and watch strategy, short courses of prednisone in case of increased bleeding symptoms. Good response documented.
• Admitted to ICU after bicycle accident with intracranial hemorrhage. Platelet count 11,000/µL.
Male 46 ys

Chronic ITP ~20-40,000/µL, bicycle accident
Initial Management

Platelet count 11,000/µL

• Platelet transfusions until bleeding stops?
• i.v. IgG 1g/kg bw
• Prednisone i.v.
• No drugs which inhibit platelet function
• No heparin
48h after admission:
platelet count 40,000 µL. CT scan no increase in bleeding. Which is the appropriate management?

a. Platelet transfusions until platelet counts are >50,000/µL?
b. Third course of i.v. IgG 1g/kg bw
c. Prednisone i.v.
d. No drugs which inhibit platelet function
e. No heparin
Patient

- Day 1 five platelet concentrates transfused until plt count increased to 35,000/μL
- i.v. IgG 1g/kg bw, day 1 and 2
- Prednisone 100 mg/day
- No heparin
- Antiepileptic drug to prevent seizures: levetiracetam (Keppra)
- Day 5: pulmonary embolism
Patients with thrombocytopenia require thrombosis prophylaxis in risk situations for DVT

Prevent thrombosis - PE!
Splenektomie

- second line treatment (after steroids) in USA, GB
- Less frequently used in Germany

Kojouri et al, Blood 2004

<table>
<thead>
<tr>
<th></th>
<th>Value</th>
<th>69%</th>
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<tbody>
<tr>
<td>CR</td>
<td>3506/5087</td>
<td></td>
</tr>
<tr>
<td>CR (5 Jahre)</td>
<td>779/1159</td>
<td>67%</td>
</tr>
<tr>
<td>relapse nach CR</td>
<td></td>
<td>15%</td>
</tr>
</tbody>
</table>

Surgical complications:

- open surgery    | 318/2465    | 12.9%        |
- laparoscopic    | 88/921      | 9.6%         |
- open surgery, fatal | 48/4955    | 1.0%         |
- Laparoscopic, fatal | 3/1301     | 0.2%         |
**Splenectomy**

- adverse effects:
  - increased risk for sepsis (life long)
  - increased risk for atherosclerosis
  - increased risk for pulmonary hypertension

---

**Sepsis**  
226 families with hereditary spherocytosis  
fatal infections = 0.73 / 1000 years (CI, 0.015-1.5)

---

**Atherosclerosis**  
144 splenectomized patients  
22 events  
Hazard ratio 5.6 (CI, 1.7-19)
**Rituximab (Anti-CD20)**

- 375 mg x m\(^{-2}\) x wk\(^{-1}\) for 4 weeks
- remission \(~\) 50%

**Symptomatic treatment**

**N-plate, Romiplostim; AMG 531 (Amgen)**

- Weekly 2-10 µg x kg\(^{-1}\)s.c

**Eltrombopag (SB-497115-GR) (GlaxoSmithKline)**

- TPO-receptor agonist (small molecule)
- oral 50-75 mg/day
Laboratory Diagnosis of ITP

Macro TP

EDTA- pseudoTP

satellitism
Free and cell-bound anti-platelet antibodies

autoantibodies

a

b

c

X
1. auto-antibodies in AITP are adsorbed by the patient’s platelets

2. platelets store IgG in the alpha granules and bind IgG via FcRIIa
Operating Characteristics of Platelet-Antibody Assays

Warkentin & Greinacher, 2001
MAIPA V.Kiefel et al. Blood 1988
(Monoclonal antibody immobilization of platelet antigens)
PAIgG: eluate (pH 2.8) testing [PIFT, GP-immunoassay]

![Diagram of PAIgG eluate process]

This technique is equivalent to GP-PAIgG testing (GPs IIb/IIIa, Ib/IX), but requires more platelets (100 x 10^6)

Platelet aab testing required?

- Aab testing usually not required
  - patients with acute, probable “post-infectious” AI TP, esp. in childhood
  - patients with uncomplicated AI TP responsive to corticosteroids, IVIG, …

- Aab testing useful
  - patients with comorbidities which can cause TP, e.g. hematologic malignancies
  - patients with refractory TP especially before institution of invasive (splenectomy), expensive/experimental therapy
Platelet Membrane Glycoprotein Polymorphisms that can cause Alloimmune Thrombocytopenia

GPIa-IIa (α2β1)
A vWf-like A(dhesion) domain (blue ball) is inserted between β–propellers 2 and 3 of the α subunit. The Br polymorphism is located between β–propellers 5 and 6 and is homologous to αvSer323

GPIIb-IIIa (αIIIbβ3)

According to PJ Newman 2001
Adapted from Humphries and Mould
Science 294:316, 2001
Alloimmune-TPs

- Neonatal AITP
- Post-Transfusion Purpura (PTP)
- acute thrombocytopenia after transfusion of platelet antibodies
- Platelet transfusion refractoriness

- important glycoproteins:
  GP Iib/IIIa, GP Ia/IIa, GP Ib/IX, Gov
Alloimmune TPs

• Major problem: HLA-antibodies

• detection of: sensitivity specificity

  free abs (plts.): ++/(+) +-  
  free abs (GP-spec): ++ ++  
  PalgG: +/- --  
  Plt-GP spec. abs +(-) ++  

  genotyping!!!
Fetal and neonatal alloimmune thrombocytopenia

FNAIT

HPA-1  a  a  b  b
Effect of random PC on platelet counts in acute NAIT
Epitope-specific monoclonal antibodies as treatment

Bakchoul T et al. Transfusion 2009
17 ± 1 days of gestation

1-8 hours after birth

Bakchoul T, et al. BLOOD 2013
<table>
<thead>
<tr>
<th></th>
<th>IgG</th>
<th>F(ab)2</th>
<th>deglykosylated-SZ21</th>
</tr>
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<tbody>
<tr>
<td><strong>Phagocytosis</strong></td>
<td>🙁</td>
<td>🌼</td>
<td>🌼</td>
</tr>
<tr>
<td>binding to FcγR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Transport to the child</strong></td>
<td>🙁</td>
<td>🙁</td>
<td>🌼</td>
</tr>
<tr>
<td>binding to FcRn</td>
<td>🙁</td>
<td>🙁</td>
<td></td>
</tr>
<tr>
<td><strong>Potential application</strong></td>
<td>🙁</td>
<td>🌼</td>
<td>🌼</td>
</tr>
<tr>
<td>postnatal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>prenatal</td>
<td>🙁</td>
<td>🙁</td>
<td></td>
</tr>
</tbody>
</table>
Recombinant HPA-1a antibody therapy for treatment of fetomaternal alloimmune thrombocytopenia: proof of principle in human volunteers


Figure 1: Platelet recovery (%) after re-injection.
Transfusion induced alloimmune thrombocytopenia

- Abrupt decrease of platelet counts following platelet or plasma transfusion
- Fever, nausea, no obvious other reason
- Blood donor (usually woman with > 2 pregnancies) had platelet allo-antibodies which are transferred with the plasma = passive immunization
Postoperative day (day 0 = day of surgery)

Platelet count (x10⁹/L)

- Transfusion of blood product
- Bacteria contaminated transfusion
- Passive alloantibody TP
Post-Transfusion Purpura

- 99.8% women preimmunized against a platelet alloantigen (usually HPA-1a)
- 7-14 days after transfusion of HPA-1a positive blood (RBCs, platelets):
  - Platelet counts <10,000/µl, bleeding
  - Pathogenesis: epitope spreading?
  - Boosted allo-antibodies crossreact with HPA-1a negative autologous platelets
- Treatment: ivIgG 2g/kg b.w.

Lubenow et al. Thromb Research, 2000;100:115-25
Transfusion Refractoriness

- Most frequent immune thrombocytopenia
- Patient develops antibodies (HLA>>HPA) which bind to transfused platelets and cause platelet destruction in the RES
Drug-induced Immune-Thrombocytopenias

- Drug-induced AITP
- Drug-dependent TP
- GP IIb/IIIa-antagonist-induced TP
- Heparin-induced TP
Drug-induced ITP

- Patients treated with gold develop ITP
- Clinical presentation, diagnosis, treatment as in ITP
- Antibody titers decrease slowly after cessation of gold. Gold treatment may cause relapse.
- GPV is the major platelet glykoprotein involved
  Garner SF et al. Blood. 2002 Jul 1;100(1):344-6
Vancomycin-Induced Immune Thrombocytopenia


Richard H. Aster and Daniel W. Bougie
Lubenow N, Hron G, Greinacher A, unpublished
## Drug-Metabolite

<table>
<thead>
<tr>
<th>Ab-class</th>
<th>TMP-SMX</th>
<th>Ex-vivo</th>
<th>none</th>
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<tbody>
<tr>
<td>Patient 1 - IgG</td>
<td>-</td>
<td>++++</td>
<td>-</td>
</tr>
<tr>
<td>Patient 1 - IgM</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Patient 2 - IgG</td>
<td>++++</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Patient 2 - IgM</td>
<td>++++</td>
<td>++</td>
<td>-</td>
</tr>
</tbody>
</table>

Kiefel et al. Transfusion 1987;27:262-265
Abciximab (ReoPro®): (chimeric Fab-fragments)

Tirofiban (Aggrastat®): (nonpeptide tyrosinderivate)

Eptifibatide (Integrilin®): (cyclic RGD-mimetic)
Thrombocytopenia after GPIIb/IIIa-inhibitor treatment

Patient R15
Patient R25

Platelet transfusion

~50% are pseudothrombocytopenia

Platelets (x 1000/µl)

h (after abciximab-bolus)
# Immune Thrombocytopenias

<table>
<thead>
<tr>
<th></th>
<th>AITP</th>
<th>PTP</th>
<th>Drug dependent TP</th>
<th>GP IIb/IIIa inhibitor TP</th>
<th>HIT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Platelet count</strong></td>
<td>variable &lt;20.000</td>
<td>&lt;10.000</td>
<td>&lt;10.000</td>
<td>&lt;10.000</td>
<td>40-80.000</td>
</tr>
<tr>
<td><strong>Bleeding symptoms</strong></td>
<td>(+) - +++</td>
<td>+++</td>
<td>+++</td>
<td>(+)</td>
<td>- - -</td>
</tr>
<tr>
<td><strong>Onset</strong></td>
<td>chronic</td>
<td>day 7-14 after transfusion</td>
<td>day 7-14 after start of drug (day 1 in case of reexposure)</td>
<td>day 1 of GPIIb/IIIa treatment (delayed onset)</td>
<td>day 5-14</td>
</tr>
<tr>
<td><strong>Thrombosis</strong></td>
<td>-- (+)</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>+++</td>
</tr>
</tbody>
</table>
Drug dependent TP: clinical management
`The Friday evening Consultant Call´

- female 67 years old, diabetic coma, renal failure, rhabdomyolysis, platelet count < 5000/µl
- Multiple blood transfusions during the last 2 weeks, 2 pregnancies
- DD: HIT? drug-dependent TP? post transfusion purpura?
- Intrafusin, structolipid, glucose, voluven, paspertin, sufenta, actrapid, liquemin, lasix, tracutil, cernevit, antra, acetylcystein, konakion, ebrantil, nitro, ciprobay, vancomycin, aterenol, vicogant, glucerna, decortin
- Stop all drugs but electrolytes, vitamins, hormons
- Start alternative antibiotics
- Start i.v. IgG and exclude PTP as soon as possible
- Reintroduce drugs sequentially after platelet counts raised