Acquired Platelet Disorders

Andreas Greinacher

Institut für Immunologie und Transfusionsmedizin
Universitätsmedizin Greifswald
Germany
Disclosures for Andreas Greinacher

In compliance with COI policy, ISTH requires the following disclosures to the session audience:

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Research Support/P.I.</strong></td>
<td>Boehringer-Ingelheim; Bayer Healthcare</td>
</tr>
<tr>
<td><strong>Employee</strong></td>
<td>No relevant conflicts of interest to declare</td>
</tr>
<tr>
<td><strong>Consultant</strong></td>
<td>Schering-Plough; Mitsubishi Pharma; Instrumentation Laboratories</td>
</tr>
<tr>
<td><strong>Major Stockholder</strong></td>
<td>No relevant conflicts of interest to declare</td>
</tr>
<tr>
<td><strong>Speakers Bureau</strong></td>
<td>No relevant conflicts of interest to declare</td>
</tr>
<tr>
<td><strong>Honoraria</strong></td>
<td>Merck, Schering-Plough, Mitsubishi Pharma, GSK, Bayer</td>
</tr>
<tr>
<td><strong>Scientific Advisory Board</strong></td>
<td></td>
</tr>
</tbody>
</table>

Presentation includes discussion of the following off-label use of a drug or medical device: fondaparinux, bivalirudin
Incidence of TP in ICU patients

12 studies
3162 patients

8 studies
2188 patients

5 studies
3104 patients

medical and surgical ICU patients combined

% of patients

<150,000/µL during ICU stay

<50,000/µL during ICU stay

<150,000/µL at admission
Patient 1

- 67 year old man
- 110 kg, diabetes
- acute coronary syndrome admission at 10.00 am
- Hb 9.5 g/dL; WBC 7,500/µL; platelet count 270,000/µL
- PCI three stents
- heparin, prasugrel, aspirin, and eptifibatide (all standard dose)
Patient 1

• 4.00 pm = 6 hours after intervention transfer to ICU because of a platelet count of 8,000/µL

• No bleeding

• Eptifibatide perfusor still running
Patient 1: What are the appropriate measures?

a. Stop all antiplatelet drugs, especially the integrilin perfusor.

b. Stop the next LMWH injection scheduled for 6.00 pm.

c. Transfuse platelets until a platelet count >15-20,000/µL is reached;

d. Give tranexamic acid to prevent bleeding.

e. Control the platelet count in citrated blood.
Patient 1: The platelet count in citrated blood is 6,000/µL. What is the appropriate management?

a. Stop all antiplatelet drugs, especially the integrilin perfusor.
b. Stop the next LMWH injection scheduled for 6.00 pm.
c. Transfuse platelets until a platelet count >10-15,000/µL is reached;
d. Give tranexamic acid to prevent bleeding.

**e. Control for aggregates in the blood smear.**
Pseudothrombocytopenia

Frequent in patients receiving GP IIbIIIa inhibitors!
GP IIbIIIa inhibitor induced pseudo-TP also occurs in citrated blood. Review the blood smear!

Treatment: educate the team
CLASSIFICATION

• (Pseudothrombocytopenia)
• Hemodilution
• Consumption
• Destruction
• Sequestration
• Decreased Production

• Impaired platelet function
CLASSIFICATION

- (Pseudothrombocytopenia)
- Hemodilution
- Consumption
- Destruction
- Sequestration
- Decreased Production
CLASSIFICATION

• (Pseudothrombocytopenia)
• Hemodilution
• Consumption
• Destruction → ITP, HIT, extracorporeal circuits
• Sequestration
• Decreased Production
CLASSIFICATION

• (Pseudothrombocytopenia)
• Hemodilution
• Consumption
• Destruction
• Sequestration
• Decreased Production

Cirrhosis (severe)
The platelet count is very dynamic, reflecting the bone marrow production of about 150 billion platelets daily.
Constant production of thrombopoietin in the liver

Bone marrow
megakaryocytopoiesis

(free thrombopoietin)

free thrombopoietin
romiplostim

Platelet count nadir

rebound of the platelet count after day 4

orthopedic surgery

cardiac surgery

Greinacher A & Selleng K; Hematology 2010
Postoperative day (day 0 = day of surgery)

Platelet count nadir

rebound of the platelet count after day 4

trauma
orthopedic surgery
vascular surgery
abdominal surgery
cardiac surgery

Greinacher A & Selleng K; Hematology 2010
Early platelet count nadir: information about magnitude of platelet consumption/severity of trauma

Recovery of plt. count: information about intact physiologic response

Postoperative day (day 0 = day of surgery)

Greinacher A & Selleng K; Hematology 2010
An early fall in platelet counts to 60,000 - 100,000/µL until day 4 after major surgery is normal
TP and Mortality

• Persistent low platelet counts are a marker for adverse outcome.

• Successful treatment of the underlying disease results in normalization of platelet counts and improved outcome.

• Does normalization of platelet counts by platelet transfusion improves outcome?

• This is unknown!
Patient 2

- Male 57 years, acute pancreatitis, alcohol induced liver cirrhosis, renal failure.
- PTT 42 sec, INR 1.9, platelet count 58.000/µl.
- Heparin 200 U/h for continuous renal replacement therapy
- After 48h: PTT 55 sec, INR 2.5, plt. 22.000/µl, bleeding at line insertions, mucosal bleeding
coagulopathy

clotting factors

platelets

100% 100%

Renal replacement artificial surface

anticoagulation

Thrombin

antifibrinolytics

bleeding
Underdosing of heparin for dialysis/ CVVH

- Coating of the artificial surface by plasma proteins
- Loss of contact phase proteins (aPTT-prolongation)
- Adhesion and activation of platelets
- Thrombin-generation
- Activated fibrinolysis
Admission due to symptomatic TP

Blood smear + differential blood count

Yes

Thrombotic thrombocytopenic purpura (TTP)

Plasmatransfusion
Plasmapheresis

No

Immune mediated
ITP, drug dependent TP,
OR
Non-immune causes
bone marrow failure
sepsis

“diagnostic“ platelet transfusion

Leukemia
Admission due to symptomatic TP

Blood smear + differential blood count

Yes

Thrombotic thrombocytopenic purpura (TTP)

Plasmapheresis

Plasmatransfusion
Emergency: isolated symptomatic TP

Transfusion of 2 platelet concentrates

Platelet count increase 0.5 - 1h after transfusion

- yes: Platelet production defect, continue transfusion
- no: Increased platelet turnover
Thrombotic Microangiopathies

Hemolytic-Uremic Syndrome

Predominantly renal

Thrombotic-Thrombocytopenic Purpura

Due to a deficiency of ADAMTS13, often antibody mediated, frequent neurologic manifestations
Thrombotic Thrombocytopenic Purpura (TTP)

• Thrombotic thrombocytopenic purpura (TTP)
  — Hereditary
  — Autoimmune
  — Inflammatory (pregnancy, post-surgery, pancreatitis)

• Miscellaneous
  — Drug (quinine, clopidogrel, cycl A, mitomycin, gemcitabine,..)
  — Transplantation-associated
  — Cancer-associated
  — HIV-associated
TTP: main symptoms

- thrombocytopenia
- hemolytic anemia (fragmented red cells)
- neurological symptoms

* Moschcowitz. Arch Intern Med 1925
von Willebrand Factor Multimers

Adapted from Fowler et al, *J Clin Invest* 76:1491-1500, 1985
vWF and platelet adhesion in TTP

Blood Flow

vWF
Platelet
Fibrinogen

vWF protease (ADAMTS13)

A1 domains
GPIb

Adhesion
≈1000 µm s⁻¹
Rolling
≈4 µm s⁻¹
Activation
≈0 µm s⁻¹
Recruitment

Regulation

≈0 µm s⁻¹
TTP Treatment

• Plasma-exchange
  – Removal of antibodies
  – Substitution of ADAMTS-13

• Plasma-transfusion

• Immunosuppression:
  – Steroids, rituximab, splenectomy
Hemolytic uremic syndrome

• Predominantly renal thrombotic microangiopathy

• Inborn defects in the complement cascade

• ~85% associated with hemorrhagic enteritis: Shigella dysenteriae serotype I or E. coli O157:H7; O104:H4
Hemolytic uremic syndrome

- Predominantly renal thrombotic microangiopathy.

- Inborn defects in the complement cascade.

- ~85% associated with hemorrhagic enteritis: Shigella dysenteria serotype I or E. coli O157:H7; O104:H4
Epidemic Profile of Shiga-Toxin–Producing Escherichia coli O104:H4 Outbreak in Germany — Preliminary Report

Christina Frank, Ph.D., Dirk Werber, D.V.M., Jakob P. Cramer, M.D., Mona Askar, M.D., Mirko Faber, M.D., Matthias an der Heiden, Ph.D., Helen Bernard, M.D., Angelika Fruth, Ph.D., Rita Prager, Ph.D., Anke Spode, M.D., Maria Wadl, D.V.M., Alexander Zoufaly, M.D., Sabine Jordan, M.D., Klaus Stark, M.D., Ph.D., and Gérard Krause, M.D., Ph.D., for the HUS Investigation Team*

Frank C. et al. NEJM, July 2, 2011; 1-11
Total 3816 patients, 855 HUS (hemolytic uremic syndrome) 54 deaths (6.3%) 88% adults Median age 42 years 68% women Incubation time 8 days

Frank C, NEJM 2011; 365:1771-1780
Treatment of severe neurological deficits with IgG depletion through immunoadsorption in patients with *Escherichia coli* O104:H4-associated haemolytic uraemic syndrome: a prospective trial

Andreas Greinacher*, Sigrun Friesecce*, Peter Abel, Alexander Dressel, Sylvia Stracke, Michael Fiene, Friedlinde Ernst, Kathleen Selleng, Karin Weissenborn, Bernhard M W Schmidt, Mario Schiffer, Stephan B Felix, Markus M Lerch, Jan T Kielstein†, Julia Mayerle†

Summary

Background In May 2011, an outbreak of Shiga toxin-producing enterohaemorrhagic *E coli* O104:H4 in northern...
PRODUCTION

Isolated thrombocytopenia
  — Alcohol
  — Hereditary

Pancytopenia
  — Numerous marrow disorders
DESTRUCTION

- Autoimmune
- Alloimmune
- Drug-dependent
Acquired platelet function defects

- Myeloproliferative disorders
- Myelodysplasia
- Liver cirrhosis
- Uremia
- Enzymatic degradation of platelet membrane receptors (plasmin, pancreatitis)
- Drugs:
  - Anti-platelet drugs
  - Serotonin reuptake inhibitors
  - Anticonvulsive drugs, valproic acid
Endothelium

Thrombin

FXa FVa

5HT

Thrombus formation

Restenosis

Bare-metal stent

Shuchman et al, NEJM 2006

TXA₂

ADP

P₂Y₁₂

ASA

Clopidogrel

Prasugrel

Ticagrelor

Patient 3

- 76 year old man
- Herniated disc with beginning paresis
- 3 month ago drug eluting stent (NSTEMI)
- aspirin 100 mg, clopidogrel 75mg, last intake in the morning
Management?

- Stop antiplatelet drugs and delay surgery until platelet function has recovered?

- Start surgery and `tolerate` the bleeding risk

- Perioperative `bridging` of antiplatelet therapy

- **Transfused platelets can only function if no active drug metabolite is present**
Irreversible platelet inhibition

- ASA
- Clopidogrel
- Prasugrel

• ASA COX-1
• Clopidogrel $P_{2}Y_{12}$ (ADP receptor)
• Prasugrel $P_{2}Y_{12}$ (ADP receptor)

• Drug effect decreases gradually over ~5 days, when new platelets are released.

Half life

- ASA 15-30 min
- Clopidogrel active metabolite present for 4-8h
- Prasugrel 7-8h
Greifswald Protocol

Thrombosis risk

Bleeding risk

ASA (+ Clopidogrel)
Last dose -24h

2 PC

Additional PC in case of bleeding

ASA

Clopidogrel + ASA

presurgery

OP

~ 6h postop

~ 12h (day 1)
postop.

Thiele T et al., JTH 2012;10:968-71
Pilot study

• 2010-2011

• 14 consecutive patients (7 females) under dual antiplatelet therapy (aspirin + clopidogrel) requiring surgery

• standardized assessment of perioperative bleeding and coronary events

Thiele et al. JTH 2012
## Outcome

<table>
<thead>
<tr>
<th>Age [years]</th>
<th>Type of surgery</th>
<th>Indication for ASA+ clopidogrel</th>
<th>Time between event and surgery</th>
<th>Bleeding complications</th>
<th>Coronary events</th>
</tr>
</thead>
<tbody>
<tr>
<td>74</td>
<td>Neurosurgery</td>
<td>DES</td>
<td>11 months</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>76</td>
<td>Neurosurgery</td>
<td>DES</td>
<td>5 months</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>54</td>
<td>Neurosurgery (renal artery stent)</td>
<td>BMS</td>
<td>9 days</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>65</td>
<td>Neurosurgery</td>
<td>STEMI</td>
<td>11 months</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>80</td>
<td>Neurosurgery</td>
<td>BMS</td>
<td>4 weeks</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>72</td>
<td>Neurosurgery</td>
<td>DES</td>
<td>3 months</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>61</td>
<td>Neurosurgery</td>
<td>DES</td>
<td>5 months</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>71</td>
<td>Orthopedic surgery</td>
<td>coronary stenosis</td>
<td>n.d.</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>84</td>
<td>Orthopedic surgery</td>
<td>transcathedral aortic valve</td>
<td>3 months</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>82</td>
<td>Orthopedic surgery</td>
<td>DES</td>
<td>6 months</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>63</td>
<td>Orthopedic surgery</td>
<td>DES</td>
<td>6 months</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>76</td>
<td>Trauma</td>
<td>DES</td>
<td>2 months</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>70</td>
<td>Urology</td>
<td>DES</td>
<td>4 months</td>
<td>prolonged bleeding</td>
<td>no</td>
</tr>
<tr>
<td>69</td>
<td>Abdominal surgery</td>
<td>DES</td>
<td>4 months</td>
<td>no</td>
<td>NSTEMI</td>
</tr>
</tbody>
</table>

Thiele et al. JTH 2012
Reversal of aspirin and clopidogrel by fresh platelets

Li et al.; JTH 2012
Less platelets to reverse aspirin?

- Transfused platelet
  - COX-1 not inhibited
  - TXA\(_2\) synthesis and release

- Aspirin inhibited platelet
  - No TXA\(_2\) synthesis
irreversible vs. reversible platelet function inhibitors
Due to the high plasma concentration of ticagrelor, transfused platelets will be inhibited for at least 48-72h, despite the short half life of 7-8h.
Patient 4: 50 y male pacemaker

- Pacemaker generator change 6 months before;
- Treated for pneumonia for 1 week, levofloxacine
- Lower limb edema, 38.5°C; WBC, 22,500/µL, 88% granulocytes, platelets 10,000/µl, no petechia, no bleeding
Blood cultures: *S. epidermidis*

- Cardiac echo: large mass engulfing the wire
- Cardiac surgery
- INR 1.7
- Fibrinogen 1.6 g/L
- D-Dimer 2.0 mg/L

**Platelet count (x10^9/L)**

- Pre
- Days after starting antibiotics

**Hospital admission**

- IV IgG
- Plasmapheresis and prednisone
- Platelet transfusions
- Heparin infusion

---

Dilution of the bacterial supernatant (x 10^2)

Factor Xa generation (%), log scale

LPS-induced factor Xa generation

Greifswald