Acquired platelet disorders
Disclosures for

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

<table>
<thead>
<tr>
<th>Research Support/P.I.</th>
<th>Johnson&amp;Johnson, Sanquin</th>
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<tr>
<td>Employee</td>
<td>No relevant conflicts of interest to declare</td>
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<tr>
<td>Consultant</td>
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<tr>
<td>Major Stockholder</td>
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<tr>
<td>Honoraria</td>
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<tr>
<td>Scientific Advisory Board</td>
<td>Asahi Kasei, Novo Nordisk, Pfizer</td>
</tr>
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</table>
coagulation abnormalities in 350 consecutive ICU patients

- moderate (PLT <100 or PT >5sec)
- severe (PLT <50 or PT >10 sec)
- any + bleeding

Levi and Opal, Crit Care 2006
thrombocytopenia: incidence and prognosis

bleeding as a cause of death in thrombocytopenia

- Platelet count <100 is associated with 2-fold increased mortality.
- Platelet count is an independent predictor of mortality.
- Mortality is only partly dependent on bleeding.

![Diagram showing mortality percentages for different platelet count ranges.](image)
Emerging evidence for platelets as immune and inflammatory effector cells

Matthew T. Rondina¹,²,³* and Olivier Garraud⁴,⁵

Binding of agonists to receptors on circulating, quiescent human platelets:
- Thrombin
- Collagen
- ADP
- Thromboxane A2
- LPS, other microbial toxins, pathogens

Triggering of signal transduction pathways leading to platelet activation

Platelet activation, aggregation, adhesion and secretion:
- Expression of platelet surface ligands such as P-selectin, integrin α₁β₃ and others
- Homotypic binding to other platelets
- Synthesis of new proteins
- Release of PF4, fibrinogen, VWF, CD40L, IL-1β, other thrombo-inflammatory factors
- Heterotypic binding to leukocytes
- Signaling leukocyte expression of prothrombotic, proinflammatory genes
- Interaction with endothelium; endothelial signaling
- Uptake and release of catecholamines
Emerging evidence for platelets as immune and inflammatory effector cells

Matthew T. Rondina\textsuperscript{1,2,3} * and Olivier Garraud\textsuperscript{4,5}
causes of abnormal coagulation in the ICU

Levi et al., Crit Care Med 2010
causes of thrombocytopenia in severe bacterial infection

1. ‘bone marrow depression’
2. DIC / consumption coagulopathy
platelet survival and Tpo-levels in bacterial infection

Folman CC et al, Thromb Haemostas 2000
hematophagocytosis

Courtesy of Bruno Francois and Frank Trimoreau, Dupuytren Hospital, Limoges, France
hematophagocytosis

- phagocytosis of blood (precursor) cells by activated histiocytes
- mediated by pro-inflammatory cytokines

50-60% ICU patients

causes of abnormal coagulation in the ICU

Levi et al., Crit Care Med 2010
thrombotic microangiopathy

- thrombocytopenia
- intravascular hemolysis (mechanically)
- fever/kidney failure/ neurologic abnormalities
microthrombosis

TTP

primary

ADAMTS13 deficiency

HUS

verotoxin-induced endothelial damage

(Malignant hypertension mechanical endothelial damage (secondary) low levels of ADAMTS-13)

DIC
cytokine-induced endothelial damage (secondary) low levels of ADAMTS-13)

ultra-large von Willebrand factor multimers
increased platelet-vessel wall interaction

increased platelet-vessel wall interaction

microthrombosis

hemolysis

organ failure
Inflammation-associated ADAMTS13 deficiency promotes formation of ultra-large von Willebrand factor

Clemens L. Bockmeyer,¹ Ralf A. Claus,¹ Ulrich Budde,² Karim Kentouche,³ Reinhard Schneppenheim,⁴ Wolfgang Lösche,¹ Konrad Reinhart,¹ and Frank M. Brunkhorst¹
Correlation between plasma activity of ADAMTS-13 and coagulopathy, and prognosis in disseminated intravascular coagulation

Jungwon Hyun\textsuperscript{a}, Hyun Kyung Kim\textsuperscript{a,b,*}, Ji-Eun Kim\textsuperscript{a,b}, Min-Gyu Lim\textsuperscript{a}, Jae Seol Jung\textsuperscript{a}, Seonyang Park\textsuperscript{c}, Han-Ik Cho\textsuperscript{a}

Thrombosis Research 124 (2009) 75–79
B

Cumulative Survival

ADAMTS13 activity ≥ 30%

ADAMTS13 activity < 30%

P (LogRank test) = 0.01

Time (days) since ICU admission
heparin and platelet count
**Pathophysiology of HIT**

**Diagram:**
- **Platelet:**
  - Alpha granule
  - PF-4/heparin complex
  - IgG

**Textual Explanations:**
- PF-4 binds to the surface of a platelet following activation.
- Complexes of heparin (GAG) and PF-4 molecules form.
- IgG binds to the PF-4/heparin complex.
- Fc stimulation leads to the generation of procoagulant-rich microparticles.
- IgG/PF-4/heparin complex activates via the Fc receptor.

*Courtesy of Dr. John G. Kelton, McMaster University; Hirsh et al. Archives Med 2004; 184:381-388.*
heparin-induced thrombocytopenia (HIT) leads to thrombosis

- may be frequently underdiagnosed?

- will lead to overt thromboembolism and/or aggravation of organ failure in majority of patients

- management by stopping heparin and replacing by alternative anticoagulant
causes of abnormal coagulation in the ICU

Levi et al., Crit Care Med 2010
the coagulopathy of bleeding

trauma

severe bleeding

insufficiently compensated loss of platelets and clotting factors

bleeding
the coagulopathy of bleeding

trauma

severe bleeding

insufficiently compensated loss of platelets and clotting factors

bleeding

+ acidosis
+ hypothermia
Trauma → Severe bleeding → Insufficiently compensated loss of platelets and clotting factors → Bleeding

Plasma expanders → Plasma dilution
- dextrans
- gelatin-based solutions
- hydroxy-ethyl starch-based solutions
LABORATORY INVESTIGATIONS

Reduced quality of clot formation with gelatin-based plasma substitutes


66% diluted NaCl 0.9%
66% diluted NaCl 0.9%

66% diluted gelofusine

66% diluted haemacell
- 8 healthy volunteers
- randomized double-blind crossover design
- 1 liter gelofusine or 1 liter 0.9% NaCl in 60 min
- outcome:
  - bleeding time
  - platelet aggregation
  - thrombin generation
thrombin generation

gelofusine
gelatin-based plasma expanders

- impairment of primary hemostasis mediated by decreased von Willebrand factor platelet adhesion

- reduced thrombin generation (due to hemodilution ?)
Hydroxyethyl starch-based solutions

- polymers of glucose units derived from amylopectin
- broad range of molecular weight
- large molecules are rapidly hydrolyzed and LMW fraction is eliminated by the kidney
- degradation dependent on degree of substitution (*hydroxyethyl* for *hydroxyl*)
Decreased circulating levels of von Willebrand factor after intravenous administration of a rapidly degradable hydroxyethyl starch (HES 200/0.5/6) in healthy human subjects

- 9 healthy volunteers
- randomized double-blind cross over design
- 1 liter 6% hydroxy-ethyl starch, DS=0.5 (Haes-Steril 6%) or albumin 5% in NaCl 0.9%
Acquired platelet defects
Acquired platelet disorders

1. Drugs

2. Systemic disorders causing platelet dysfunction
## Drugs affecting platelet function

### Thrombolytic Agents
- Streptokinase
- Urokinase
- Tissue Plasminogen Activator (TPA)

### Miscellaneous
- Clofibrate
- Dextran
- Guaifenesin (expectorant)
- Radiographic contrast media

### Food/Herbs (at high concentrations)
- Alcohol
- Caffeine (methylxanthine)
- Cumin
- Dong quai
- Fenugreek
- Garlic, onion, ginger
- Ginseng
- Fish Oil
- Tamarind
- Turmeric
- Willow
- Vitamins C and E
Drugs affecting platelet function

- Antiplatelet, anticoagulant and thrombolytic agents
- Antibiotics (β-lactam, cephalosporins, amphotericine, hydrochloroquins)
- Calcium channel blockers
- Selective serotonin-reuptake inhibitors
- Some local and general (halothane) anaesthetics
Diseases affecting platelet function

- Uremia
- Cardiopulmonary bypass
- Myeloproliferative disease
- Liver cirrhosis
- HIV
- Paraproteinemias
Uremic Thrombocytopenia Is not about Urea

Gabor E. Linthorst,* Hans J. Avis, † and Marcel Levi ‡

<table>
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<tr>
<th>Parameter</th>
<th>Blood Urea (mg/dl)</th>
<th>Blood Creatinine (mg/dl)</th>
<th>Urea Clearance (ml/min)</th>
<th>Creatinine Clearance (ml/min)</th>
<th>Hemoglobin (g/dl)</th>
<th>Ivy Bleeding Time (minutes)</th>
<th>PFA Epi (seconds)</th>
<th>PFA ADP (seconds)</th>
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<td>Normal values</td>
<td>&lt;20</td>
<td>&lt;1.2</td>
<td>&gt;80</td>
<td>&gt;90 for males, &gt;80 for females</td>
<td>&gt;13 for males, &gt;12 for females</td>
<td>2.5 to 7.5</td>
<td>&lt;118</td>
<td>&lt;200</td>
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<td>Patient values</td>
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<td>(age in years)</td>
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<td>Father (59)</td>
<td>10.4</td>
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<td>Mother (59)</td>
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<td>79</td>
<td>13.4</td>
<td>ND</td>
<td>73</td>
<td>ND</td>
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ND, not done; PFA Epi, Platelet Function Analysis towards epinephrine.
Cardiopulmonary Bypass Circuit Causes Platelet Activation
Platelet dysfunction in cardiopulmonary bypass

- Extracorporeal circuit
- Priming with plasma expanders
- Heparin, aspirin
- Shedding of surface glycoproteins by activated proteases
How to assess platelet function?

- Born light-transmission aggregometry
- PFA-100
- Electron microscopy
- Bleeding time
- Clot retraction
- Multiplate
- VerifyNow
- VASP
- RoTEM
- TEG (platelet mapping)
- CS-2500
Bleeding Time

- Standardised incision on the skin, and timing how long it takes the patient to stop bleeding
- **Ivy template method**
- Sphygomanometer inflated on arm to 40mmHg.
- 10mm long 1mm deep incision using a template.
- Mop up blood with filter paper every 30 seconds; measure the time it takes to stop bleeding
- Normal less than 9½ minutes
Bleeding Time = obsolete

BCSH guidelines 2011: The BT is highly dependent on operator technique, is subjective and is influenced by patient variables unrelated to haemostasis, such as age, gender, haematocrit, vascular pattern, skin thickness and skin temperature.

The BT therefore has poor reproducibility, sensitivity and specificity, as well as being invasive; for these reasons the bleeding time is not recommended (1B)

Platelet aggregrometry
Platelet function – LTA

- Light transmission Aggregometry - Born (1962)

- Comparison in optical density between platelet rich plasma and platelet poor plasma

- OD changes (increases) as platelet aggregate
Platelet aggregrometry
Platelet function analyzer (PFA-100)
VERIFYNOW Point of Care Test

It measures the rate and extent of changes in light transmittance caused by platelet aggregation in a pre-set tube in which whole blood is placed.

It thus mimics light transmission aggregometry.

Samples containing inhibited platelets will produce low level of light transmittance while samples containing normally functioning platelets will aggregate more rapidly, resulting in higher level of light transmittance.
Platelet reactivity and clinical outcomes after coronary artery implantation of drug-eluting stents (ADAPT-DES): a prospective multicentre registry study

Gregg W Stone, Bernhard Witzenbichler, Giora Weisz, Michael J Rinaldi, Franz-Josef Neumann, D Christopher Metzger, Timothy D Henry, David A Cox, Peter L Duffy, Ernest Mazzaferrri, Paul A Gurbel, Ke Xu, Helen Parise, Ajay J Kirtane, Bruce R Brodie, Roxana Mehran, Thomas D Stuckey, for the ADAPT-DES Investigators*
Management of platelet dysfunction

- Treat the underlying disorder
  - Discontinue drug
  - Dialysis & use of EPO
  - Reduce paraprotein
  - … etc.

- Platelet transfusion

- DDAVP
DDAVP
(De-amino D-Arginine Vasopressine)

- release of von Willebrand multimers
- improvement of primary hemostasis
- shortening of the bleeding time
## DDAVP: evidence-based indications

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Acquired platelet disorders