BITE STUDY

BLEEDING IN THROMBOCYTOPENIA EXPLAINED

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Bleeding in hemato-oncology patients

- Severe thrombocytopenia due to disease and / or treatment
- Incidence of bleeding varies from 5%-70%
- Stringent daily bleeding assessment in high intensity chemotherapy / allogenic SCT → 90% reported bleeding [1]
  - 56% WHO grade ≥ 2
  - 7.8% serious: WHO grade 3-4

1. Ypma et al, Transfus Med. 2012 Dec;22(6):426-31.

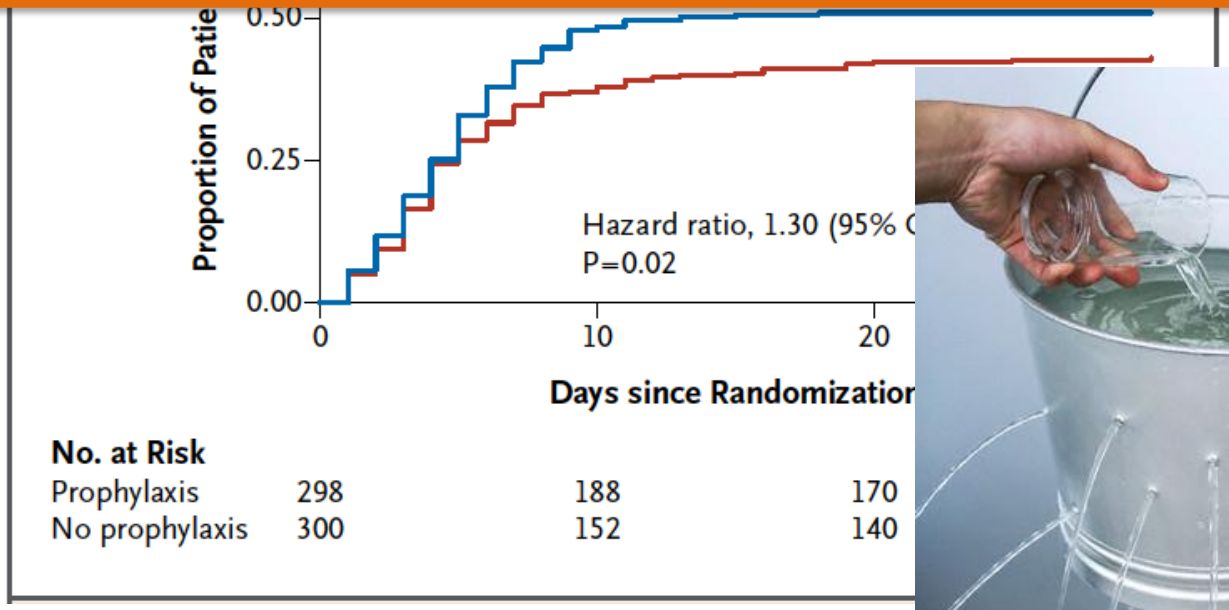
Prevention of bleeding

- Clinical practice: prophylactic platelet transfusion < $10x10^9$ /L
- 67% of all platelet transfusions are in the hemato-oncology population[1]
  - 2/3 prophylactic transfusions
- Disadvantage frequent transfusion
  - Complications
  - Costs
  - Availability blood products

Estcourt et al, Vox Sang. 2012 Nov;103(4):284-93

Prophylactic vs therapeutic platelet transfusion RCT

43% bleeds despite prophylaxis
50% does not bleed without prophylaxis



Stanworth et al, N Engl J Med 2013;368:1771-80.

Subanalysis

	N (%)	Prophylaxis (% bleeding)	Therapeutic (% bleeding)
Chemo / allo SCT	179 (30%)	38%	58%
Auto SCT	421 (70%)	45%	47%

HR 1.43 (1.19-1.72) p=0.001

- RBC transfusion < 3 days
- Female sex
- Fever > 38 in 3 days
- PLT count 0-20
- Duration low platelet count < 10 3 dg

Stanworth et al, Haematologica 2015 Jun;100(6):740-7
Stanworth et al, Transfusion 2014 Oct;54(10):2385-93

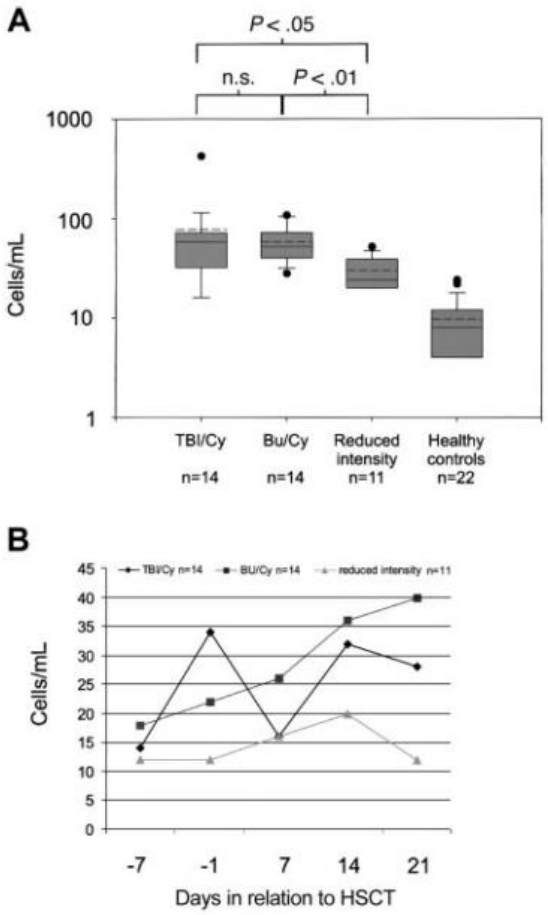
Pathophysiology of bleeding in hemato-oncology patients

- Pathophysiology of bleeding in hemato-oncology patients not fully explained by platelet count

- Other probable important players
  - Endothelial cells
  - Platelet function
  - Coagulation / fibrinolysis
  - Inflammation

Endothelial damage

- Chemotherapy – endothelial damage[1]
- Thrombocytopenia – endothelial damage[2]
- Chemotherapy – microalbuminuria [3]



1. Woywodt et al, Blood, 2004. 103(9): p. 3603-5.
2. Kitchens et al, Blood, 1975. 46 (4): p. 567-78
3. Morito et al, Bone Marrow Transplant, 2013. 48(7): p. 972-6

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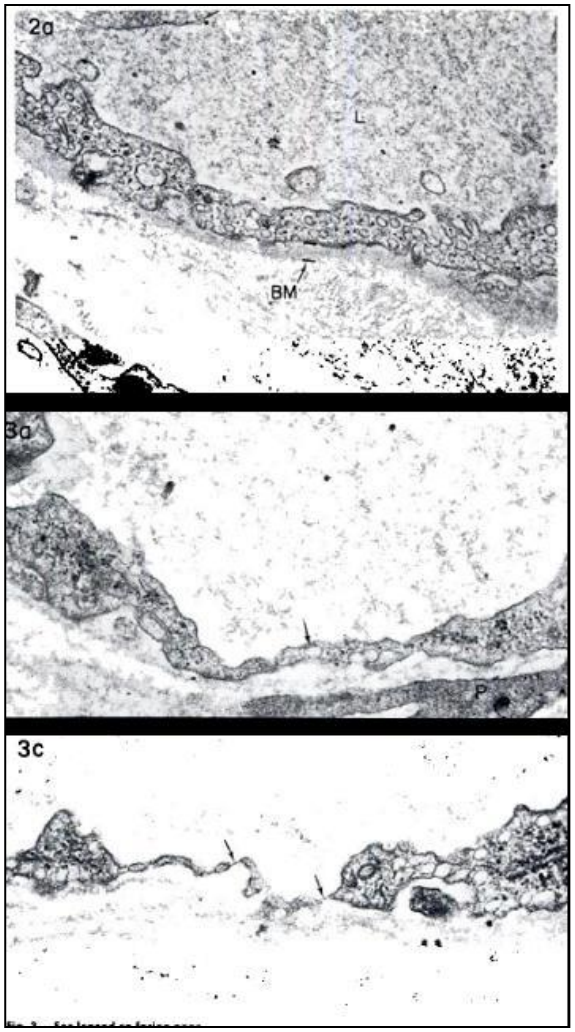

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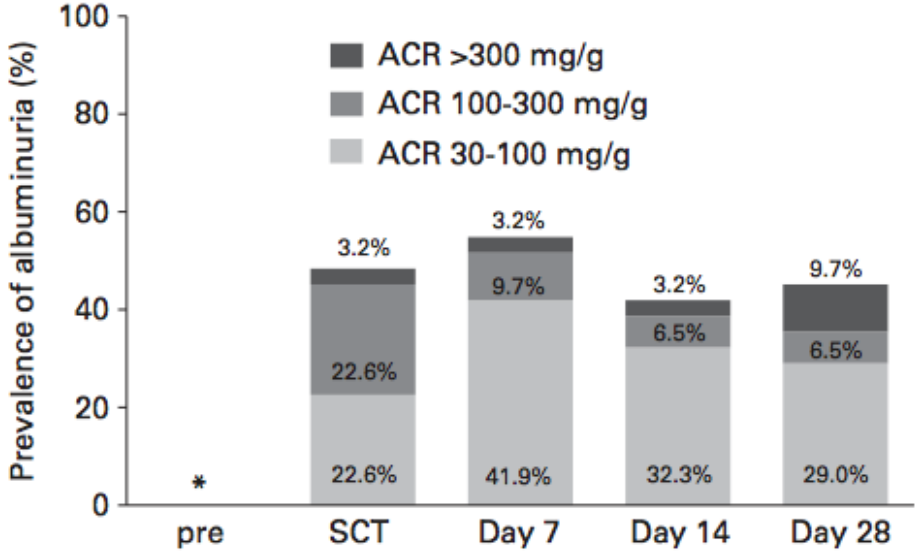

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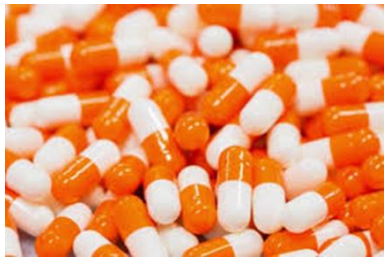
The BITE study - Objectives

- Identifying hemato-oncology patients with a high bleeding risk
  - By identifying **different risk factors** and their contributions to bleeding risk






The BITE study - Objectives

- In future: better preventive strategies

Study population

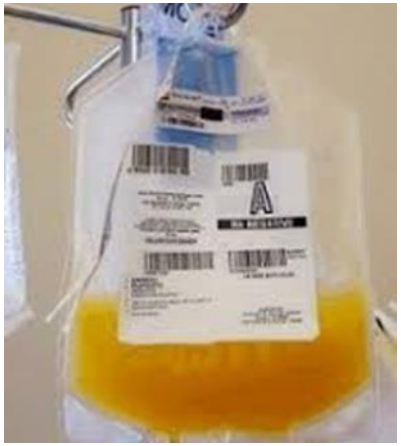
- All (expected) **thrombocytopenic hemato-oncology patients** likely to receive **prophylactic platelet transfusions**
  - Including MDS, MF, AA

- Inclusion
  - Patients ≥ 18 years
  - Admission at hemato-oncology ward
  - Hemato-oncologic disease or MDS, myelofibrosis, aplastic anemia

- Exclusion for reporting
  - None

BITE study – cases

- Clinically relevant bleeding events
  - First relevant bleeding per admission



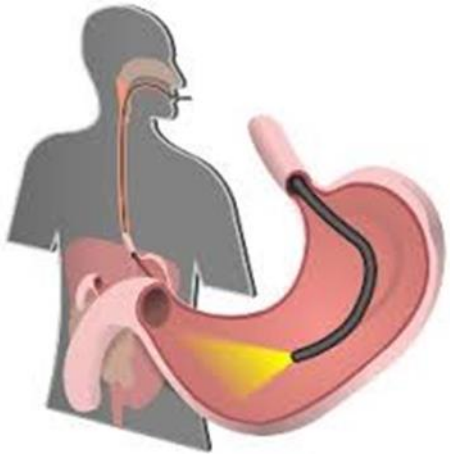


Table 2. Summary of the Modified WHO Bleeding Scale*

WHO Bleeding Grade	Examples
1	Oropharyngeal bleeding ≤30 min in 24 h Epistaxis ≤30 min in previous 24 h Petechiae of oral mucosa or skin Purpura ≤1 inch in diameter Spontaneous hematoma in soft tissue or muscle Positive stool occult blood test Microscopic hematuria or hemoglobinuria Abnormal vaginal bleeding (spotting)
2	Epistaxis >30 min in 24 h Purpura >1 inch in diameter Joint bleeding Melanotic stool Hematemesis Gross/visible hematuria Abnormal vaginal bleeding (spotting) Hemoptysis Visible blood in body cavity fluid
3	Bleeding at invasive sites Bleeding requiring red blood cell transfusion over routine transfusion needs Bleeding associated with moderate hemodynamic instability
4	Bleeding associated with severe hemodynamic instability Fatal bleeding CNS bleeding on imaging study with or without dysfunction

CNS = central nervous system; WHO = World Health Organization.
* From references 18 and 22.

Nationwide case control study

- Epidemiologic study:
  - Clinical risk factors
  - Standard diagnostics
  - Match cases to controls who did not bleed
    - Therapy
    - Hospital and time

- Additional laboratory study: citrate and urine samples
  - Investigate endothelial biomarkers in bleeding vs non bleeding patients
    - Before chemo-course (2th course) and before /after platelet transfusion
  - Most promising biomarkers will be selected from separate laboratory study
    - AML vs autologous SCT → samples from entire treatment period

Participating centers

Epidemiological part:

- List of all eligible admitted patients
  - Patient ID (in hospital only)
  - Diagnosis
  - Date of admission and discharge
  - Indication admission
  - If applicable: cause of death

Participating centers

Epidemiological part:

- Report cases: patients with clinical relevant bleeding
  - Date of bleeding
  - Location and grade of bleeding
  - Interventions for bleeding

- Preferable : Short questionnaire → informed consent needed
  - Previous bleeding events
  - Family history

- Control selection and data-extraction medical records: BITE-team

Participating centers

Laboratory part:

- Same patient list of admissions and reporting of cases

- Collect samples of all possible eligible patients
  - Informed consent (including questionnaire)
  - Obtain samples citrate plasma and urine, at least :
    - One sample before chemo (2th course)
    - One sample before first platelet transfusion of that course
    - One sample the morning after first platelet transfusion
  - OR if possible citrate plasma twice a week at routinely lab

  - If possible: platelet activation flow cytometric assays

  - Store samples until case is present /controls have been selected
    - minimum one year
    - Microalbuminuria test local if possible

Logistics

- Digital data collection where possible
  - Medical intelligence, data warehouse, IT-department
  - Data:
    - clinical chemistry
    - transfusion data
    - microbiology/virology data
    - pharmaceutic data
- Laboratory samples
  - Arrangements for (automatic) orders for samples
  - Arrangements for storage
- METC procedure in LUMC
  - Local approval procedures?
- Account for researcher / research nurse

BITE study

- Planned start: fall 2017

Subanalysis TOPPS

- RBC transfusion < 3 days

  HR 1.24 (1.03-1.50) p=0.02
- Female sex

  HR 1.33 (1.10-1.61) p=0.0002
- Fever > 38 in 3 days

  HR 1.7 (1.3-2.4) p =0.03
- PLT count 0-20

  HR 9.77 (3.35-28) p=0.0002
- Duration low platelet count < 10 3 dg

  HR 3.71 (2.39-5.76) chemo/allo

Sample size

- Cases: estimated 150/year in hospitals who are willing to participate → Aim: 150-200 cases

- Controls: aim for 4 controls per case