CCM tutorial

# Clinical Haematology in ICU

16 June 2015

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# Topics

- Neutropenic fever
- Treatment aim for hematology patients
- Post HSCT complications
- Thrombocytopenia for ICU care
- Management of uraemic bleeding
- Prophylactic/ therapeutic platelet transfusion in hematological cancer patients

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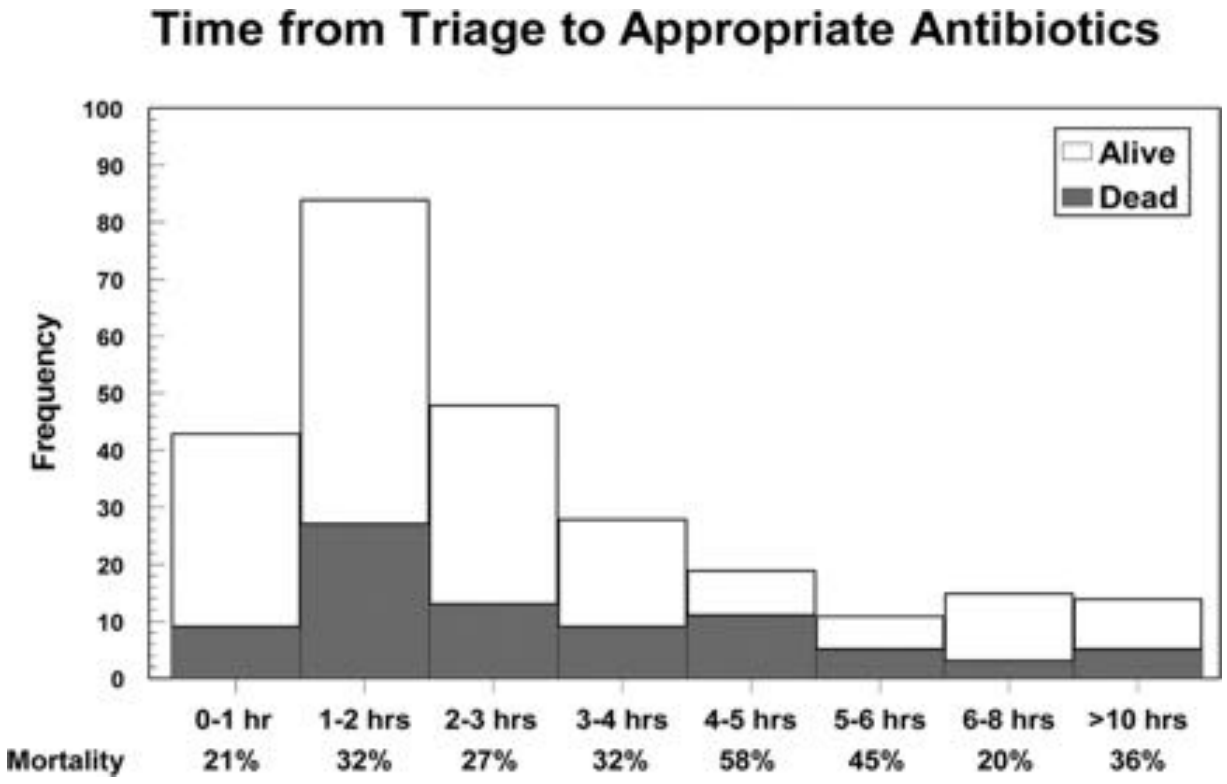
# Neutropenic fever

- Definition: Temp > 38 degree C
  - Severe neutropenia: ANC < $0.5 \times 10^{9}$/L
  - Profound neutropenia: ANC < $0.1 \times 10^{9}$/L
- Increase risk if Day 1 absolute lymphocyte count of less < $0.7 \times 10^{9}$/L
- Nadir neutrophil: day 10-14 post chemo
  - Oral and GI mucositis
  - Activation of nuclear factor-kB & proinflammatory cytokines
  - ↑ epithelial cell apoptosis
  - ↑ mucosal permeability
  - Translocation of microorganisms from pool of bacterial and fungi colonizing the gut

# Septic shock: Antibiotics door-to-needle time correlates with mortality




There was a significant association **<1 hr** time cutoff

- Mortality 19.5 vs. 33.2%
- OR 0.30
- 95% CI, 0.11–0.83
- *p =0 .02*

Critical Care Medicine: 38(4), April 2010: 1045-1053

# Fever in hematology patients

- Graft-*versus*-host disease
- Differentiation syndrome
- Tumour lysis syndrome
- Tumour-related fever
- Antibiotic/medication-related fever

Fig 1. Conditions that may mimic sepsis in haematology patients.

1. Endocarditis
2. Sinusitis
3. Skin/soft tissue
4. Intravenous catheter
5. Osteomyelitis
6. Perforated viscus
7. Neutropenic enterocolitis
8. Meningitis
9. Empyema

Fig 3. Occult sources of infection.

BJH, 2010: 152, 380–391

# Use of GCSF/ antimicrobial prophylaxis in neutropenic hematology patients

**GCSF:**

- ✔In AML
  - Stimulation of myeloid blast cells has not been shown clinically relevant in studies
  - At induction: Reduce days of neutropenia and infection complications in older patients > 55 (long term outcome not changed)
  - After CR (post consolidation)
- ✔ALL/ lymphoma
- ✗ Priming leukaemic cells before chemo
- ✓During febrile episode: use in certain high-risk febrile neutropenic patients in pneumonia, hypotension, MOF or fungal infection. ASCO: GCSF should not be routinely used as adjunctive treatment with antibiotic therapy for patients with fever and neutropenia
- Post HSCT: Use can increase risk of engraftment syndrome

**Prophylactic antimicrobials:**

- A quinolone + an anti-fungal in all hematological malignancies if there is expected neutropenia < $1.0_{X}\ 10^{9}$/L for more than 7 days

JCO, 2000(24): 3187–3205

# Use of IVIG in hematology patients

- **Immune-mediated cytopenia**
- **CLL/ lymphoproliferative diseases** with hypogammaglobulinaemia : treatment and prophylaxis
- **Myeloma with immunoparesis**: Infective episodes of myeloma / Prophylaxis in cases with recurrent respiratory infection
- **After HSCT**: Immunomodulation after HSCT/ Herpes zoster infection
- *Risk:*
  - *Anaphylactoid reaction in IgA deficiency*
  - *Thrombosis*
  - *Renal failure*
    - *Transient vascular ischemia due to a reduction in renal perfusion by immune complex deposition*
    - *Vacuolization plus swelling of the renal tubular epithelium by osmotic stress (sucrose preparation)*

- ****** for slow infusion***

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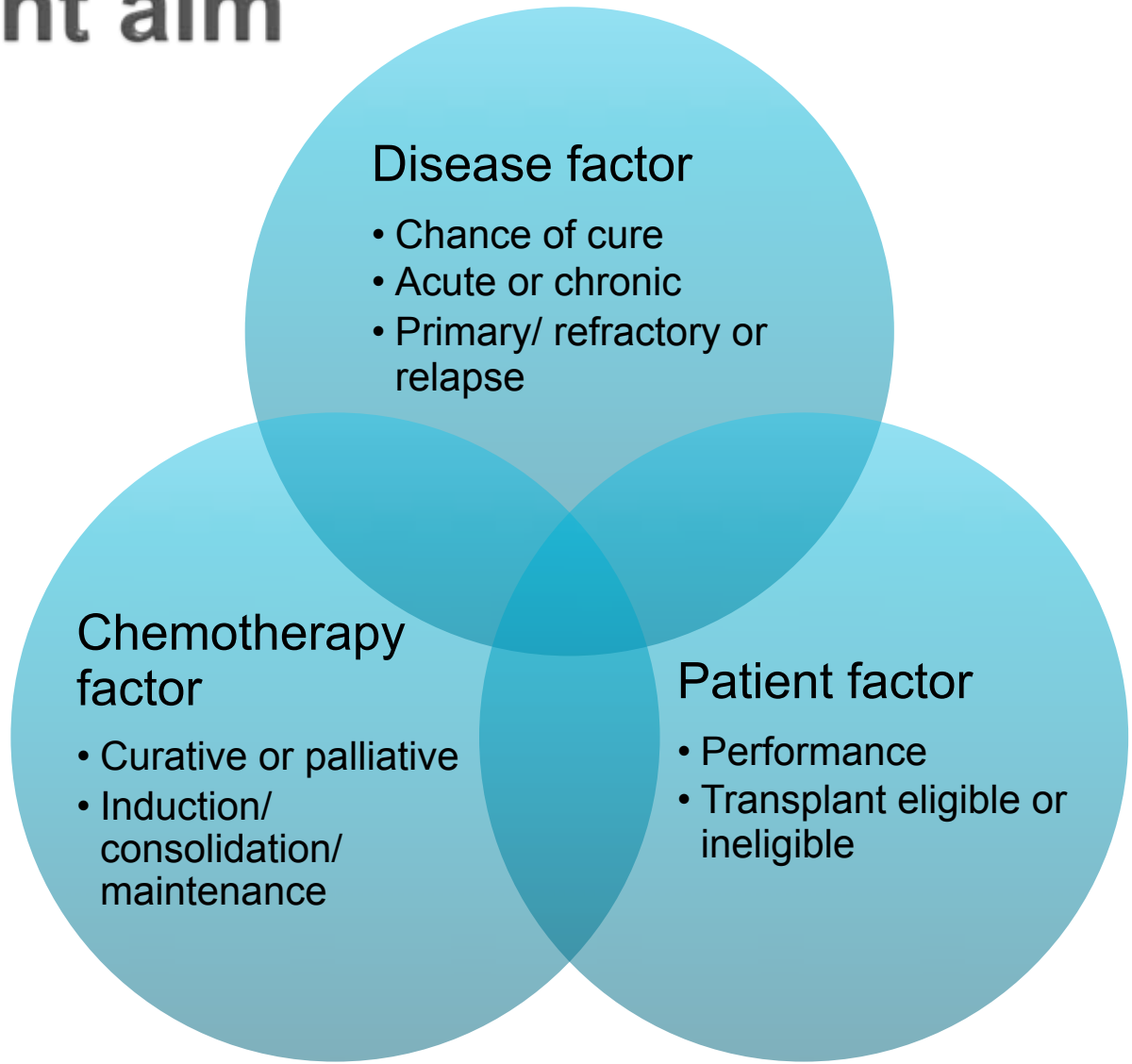
# Hematological Oncology: Treatment aim



# Recommended timing for Hematopoietic Stem Cells Transplant (HSCT) referral

## Adult Leukemias and Myelodysplasia

### Acute Myelogenous Leukemia (AML)

*High resolution HLA typing is recommended at diagnosis for all patients*

Early after initial diagnosis, all AML patients including:
- CR1—except favorable risk AML (defined as: t(16;16); inv 16; t(8;21); t(15;17); normal cytogenetics with NPM1 or biallelic CEBPA mutation and without FLT3-ITD)
- Antecedent hematological disease (e.g., myelodysplastic syndrome (MDS))
- Treatment-related leukemia
- Primary induction failure or relapse
- Presence of minimal residual disease after initial or subsequent therapy
- CR2 and beyond, if not previously evaluated

### Acute Lymphoblastic Leukemia (ALL)

*High resolution HLA typing is recommended at diagnosis for all patients*

Early after initial diagnosis, all ALL patients including:
- CR1
- Primary induction failure or relapse
- Presence of minimal residual disease after initial or subsequent therapy
- CR2 and beyond, if not previously evaluated

### Myelodysplastic Syndromes (MDS)

Any intermediate or high IPSS score

Any MDS with poor prognostic features, including:
- Treatment-related MDS
- Refractory cytopenias
- Adverse cytogenetics
- Transfusion dependence

### Chronic Myelogenous Leukemia (CML)

- Inadequate hematologic or cytogenetic response to tyrosine kinase inhibitor (TKI) therapies
- Disease progression
- Intolerance to TKI therapies

- Accelerated phase
- Blast crisis (myeloid or lymphoid)

### Chronic Lymphocytic Leukemia (CLL)

- High-risk cytogenetics or molecular features (e.g., del(11q) or del(17p); ZAP70, CD38 positivity; unmutated Ig VH mutational status)
- Short initial remission
- Poor initial response
- Fludarabine-resistant
- Richter's transformation

## Lymphomas

### Non-Hodgkin Lymphoma

Follicular
- Poor response to initial treatment
- Initial remission duration <12 months
- First relapse
- Transformation to diffuse large B-cell lymphoma

Diffuse Large B-Cell or High-Grade Lymphoma
- At first or subsequent relapse
- CR1 for patients with high or high-intermediate IPI risk
- No CR with initial treatment
- Second or subsequent remission

Mantle Cell
- After initiation of therapy

Other High Risk Lymphomas
- After initiation of therapy

### Hodgkin Lymphoma

- Primary induction failure or relapse
- Second or subsequent remission

## Multiple Myeloma

### Multiple Myeloma

- All patients after initiation of therapy
- At first progression

### Severe Aplastic Anemia and other marrow failure syndromes

(including Fanconi anemia, Diamond-Blackfan anemia, and others)

- At diagnosis

National Marrow Donor Program®/Be The Match® and the American Society for Blood and Marrow Transplantation

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# Engraftment syndrome

- 7-59% post HSCT; Mortality 25%
- Within 96 hours following engraftment
- Fever, rash, non cardiogenic pulmonary edema
- Hepatic/ renal failure/ weight gain/ transient encephalopathy/ shock and multi-organ failure
- Rapid ↑ in WBC count
- Rapid ↑ of cytokines
- ↑ Prevalence by use of GCSF
- Mx: Supportive/ steroid

Current Anaesthesia & Critical Care (2008) 19, 80–90

# Diffuse alveolar haemorrhage (DAH)

- Incidence 5%; mortality 72%
- Within 1st 30 days
- Auto > allo BMT; Correlates with marrow recovery
- Dyspnea, cough, pyrexia and hypoxaemia, haemoptysis is rare
- CXR:
  - Bilateral interstitial and alveolar infiltrates, perihilar and bibasal, may precede clinical symptoms by 3 days
- HRCT:
  - bilateral ground glass infiltrate
- BAL:
  - Progressively bloodier samples and later only haemosiderin-laden macrophages
- Risk factors
  - prior intensive chemo, TBI, old age, renal insufficiency, WBC recovery
- Pathogenesis:
  - small vessel endothelium injury
  - Thrombotic microangiopathy due to chemo
  - pulmonary neutrophil influx
  - Alveolitis due to acute GVHD
  - Mediated by IL 12 and TNF-α
- Mx: supportive and high dose steroid.
- Death: sepsis and MOF rather then respiratory failure

Current Anaesthesia & Critical Care (2008) 19, 80–90

# Idiopathic pulmonary syndrome (IPS)

- Incidence 10%; mortality 74%
- Occurs in 1st 2 months
- Diffuse lung injury without infective cause found
- Risk factors: age, non leukaemic malignancy, positive donor CMV serology, high dose chemo, TBI, MOF; reduced risk by non-myeloablative chemo regimen
- Auto: caused by high dose chemo; allo: acute GVHD which is immune mediated
- Supportive, steroid unproven
- Death: infection and respiratory failure

Current Anaesthesia & Critical Care (2008) 19, 80–90

# Bronchiolitis obliterans organising pneumonia (BOOP)

- Incidence 1.4%; mortality 21%
- Caused by GVHD esp after allo BMT
- Within 1-3 months after HSCT
- Symptoms:
  - Dyspnea, dry cough, pyrexia, acute respiratory failure requiring mechanical ventilation
- BAL:
  - Intraluminal granulation with fibroblasts in small airways, alveolar ducts and alveoli; infiltration of interstitium by lymphocytes & macrophages, no organisms can be cultured (distinct from pneumonia)
- HRCT:
  - Patchy consolidation and ground glass changes
- Treatment: long term steroid
- Distinctive from Bronchiolitis Obliterans
  - Occurs later after acute phase
  - Inflammation of small airways lead to progressive obstruction
  - Deteriorates over months/ years
  - Steroid limited response

Current Anaesthesia & Critical Care (2008) 19, 80–90

# Cardiac failure

- Risk factor: pre HSCT LVEF < 50%, VOD, severe sepsis, acute renal failure and fluid overload secondary to renal failure
- Cardiotoxic :
  - Chemo: Anthracycline, cisplatin, etoposide, cyclophosphamide
  - Stem cells preservatives: DMSO
- CTX: dose dependent (> 120mg/kg), coronary endothelial cells are most sensitive, leading to MI
- Differentiating between cardiogenic pulmonary edema and other causes
- Treatment: diuretics, ACEI, inotropes

Current Anaesthesia & Critical Care (2008) 19, 80–90

# Veno-occlusive disease (VOD)

- Incidence 20-50%; mortality 20-50%
- Thrombosis of small central hepatic venules following endothelial cell damage from high-dose chemotherapy (sinusoidal obstruction syndrome)
- Within 1st 21 days after HSCT
- Risk factors:
  - Conditioning regimen particularly busulfan and melphalan,
  - age,
  - raised pre-transplant ALT,
  - use of gemtuzumab ozogamicin,
  - alloBMT for leukaemia beyond second relapse or second transplant
- Diagnosis:
  - mainly clinical;
  - hepatic doppler USG reduced or reverse portal blood flow,
  - In theory hepatic venous pressure gradient > 10mmHg; liver biopsy of high risk of haemorrhage
- Treatment:
  - supportive,
  - minimize renal and hepatotoxic drugs
  - avoid low-dose dopamine that reduce splanchnic blood flow
  - water and sodium balance
  - diuretics + paracentesis for ascites, pain and infection
  - TPN may cause additional liver damage
  - Correct coagulopathy
- Death: hepatic and renal dysfunction, MOF, respiratory failure

Current Anaesthesia & Critical Care (2008) 19, 80–90

# VOD

## 1. Establish diagnosis (Seattle or Baltimore criteria)

| Modified Seattle criteria | Baltimore criteria |
| --- | --- |
| At least two of the following, occurring within 20d of transplantation:<br>• Serum bilirubin > 34 umol/L (> 2mg/dL)<br>• Hepatomegaly with right upper quadrant pain<br>• > 2% weight gain from baseline due to fluid retention | Serum bilirubin > 34 umol/L (> 2mg/dL) within 21d of transplantation AND at least two of the following:<br>• Hepatomegaly<br>• > 5% weight gain from baseline<br>• Ascites |

Ann Intern Med. 1993 Feb 15;118(4):255-67.

Transplantation. 1987 Dec;44(6):778-83.

# VOD (severity)

2. Determine severity (Seattle criteria)

| | |
|---|---|
| Mild | No adverse effects of liver disease, AND<br>No medications required for diuresis or hepatic pain, AND<br>All symptoms, signs and laboratory features reversible |
| Moderate | Adverse effects of liver disease present, AND<br>Sodium restriction or diuretics required, OR<br>Medication for hepatic pain required, AND<br>All symptoms, signs and laboratory features reversible |
| Severe | Adverse effects of liver disease present, AND<br>Symptoms, signs or laboratory features not resolved by day +100, OR<br>Death |

Biol Blood Marrow Transplant. 2011 Nov;17(11):1713-20.

# Neurological

- CVA:
  - Bleeding due to thrombocytopenia
  - Thrombosis due to DIC
- CNS infection
- Metabolic encephalopathy
  - Confusion/ seizure
  - Metabolic disturbance
  - Wernicke (ataxia and opthalmoplegia) due to thiamine deficiency/ gut GVHD causing malabsorption
- Treatment related neuropathy
  - CsA: PRES: headache, confusion, ↓ level of consciousness, visual changes and seizures. MRI shows posterior cerebral white matter edema
  - OKT3: aseptic meningitis
  - Steroid: psychosis, myopathy, withdrawal complications
- Chronic GVHD: polyneuropathy, polymyositis and MG

Current Anaesthesia & Critical Care (2008) 19, 80–90

# Infection risk post transplant

| Type of Hematopoietic Stem Cell Transplant | Source of Stem Cells | Risk of Early Infection: Neutrophil Depletion | Risk of Late Infection: Impaired T and B Cell Function | Risk of Ongoing Infection: GVHD and Iatrogenic Immunosuppression | Graft versus Tumor Effect |
|---|---|---|---|---|---|
| Autologous | Recipient (self) | High risk; neutrophil recovery sometimes prolonged | ~1 year | Minimal to no risk of GVHD and late-onset severe infection | None (–) |
| Syngeneic (genetic twin) | Identical twin | Low risk; 1–2 weeks for recovery | ~1 year | Minimal risk of GVHD and late-onset severe infection | +/– |
| Allogeneic related | Sibling | Low risk; 1–2 weeks for recovery | ~1 year | Minimal to moderate risk of GVHD and late-onset severe infection | ++ |
| Allogeneic related | Child/ parent(haploidentical) | Intermediate risk; 2–3 weeks for neutrophil recovery | 1–2 years | Moderate risk of GVHD and late-onset severe infection | ++++ |
| Allogeneic unrelated adult | Unrelated donor | Intermediate risk; 2–3 weeks for neutrophil recovery | 1–2 years | High risk of GVHD and late-onset severe infection | ++++ |
| Allogeneic unrelated cord blood | Unrelated cord blood units (x2) | Intermediate to high risk; neutrophil recovery sometimes prolonged | Prolonged | Minimal to moderate risk of GVHD and late-onset severe infection | ++++ |
| Allogeneic mini (nonmyeloablative) | Donor (transiently coexisting with recipient cells) | Low risk; neutrophil counts close to normal | 1–2+ years | Variable risk of GVHD and late-onset severe infection | ++++ (but develops slowly) |

**Table 1:** Infection risk associated with type of transplant.

Kedia et al., J Stem Cell Res Ther 2013, S3

# Infection risk post transplant

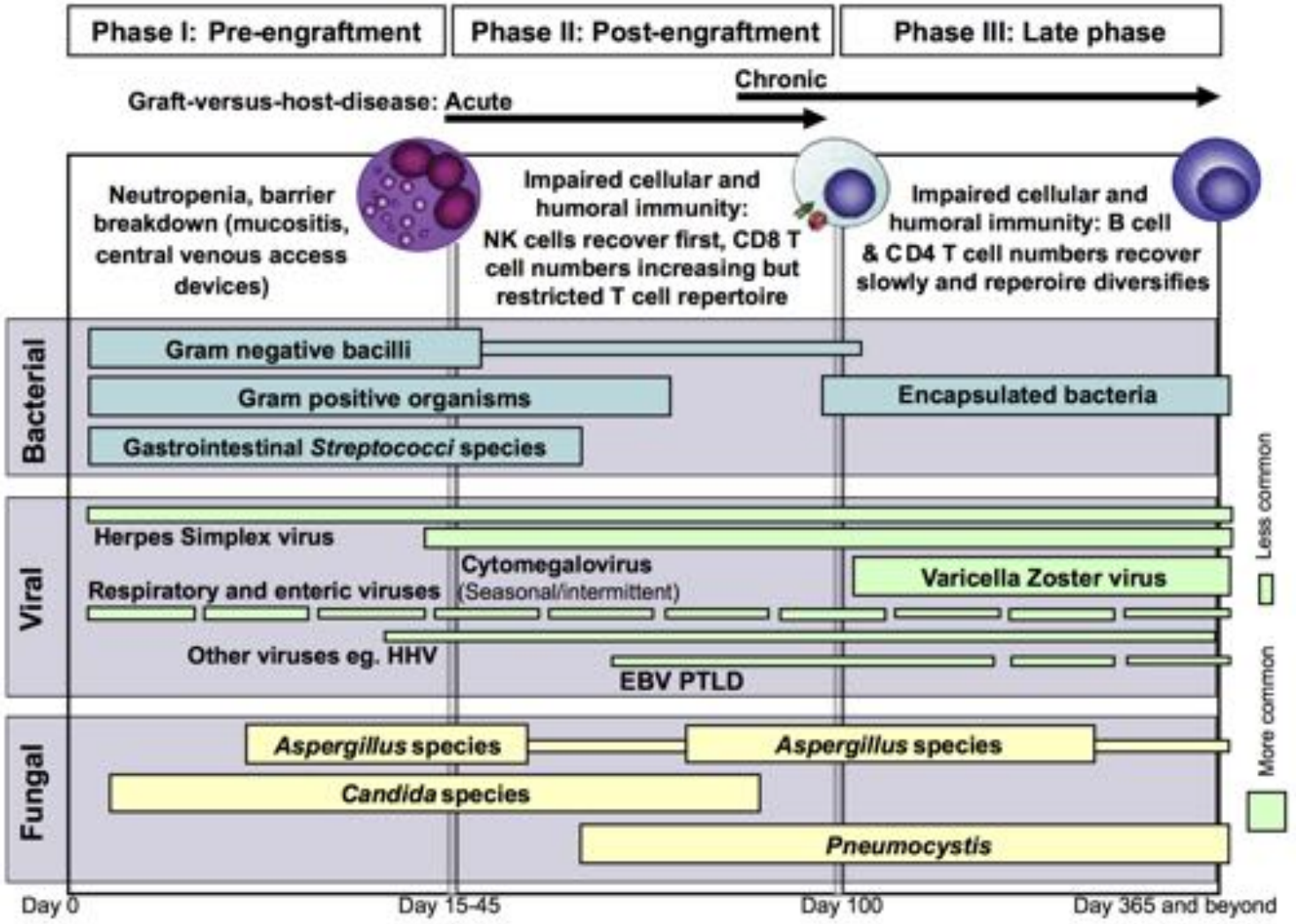


**Figure 1:** Phases of opportunistic infections among allogeneic HSCT recipients.

Kedia et al., J Stem Cell Res Ther 2013, S3

# GVHD

- Acute vs chronic (before and after 100 days)
- Triad: 1.dermatitis, 2.hepatitis, 3.enteritis
- Skin rash, colicky abdominal pain, voluminous secretory diarrhoea, nausea and vomiting, ileus and GIB
- Diagnosis: clinical
- Treatment: immunsuppressant, octreotide
- Death: mostly related to infection

Current Anaesthesia & Critical Care (2008) 19, 80–90

# Haematological

- TTP
- Inherited or immune-mediated
  - Disorder of coagulation system
  - Inhibition or deficiency of ADAMTS13 (metalloprotease that cleaves vWF)
  - Reduced ADAMTS13 activity leads to large multimers of wVF
  - Encourage platelet aggregation of clot formation

- Post HSCT
  - Not be related to ADAMTS13
  - Propose to be due to endothelial damage by chemo of CsA lead to release of cytokines such as TNF-α precipitating a prothrombotic status
  - Risk for post HSCT TTP: old age, female, HLA mismatch, high grade acute GVHD, CsA Rx, history of severe infection
  - Vastly different response to TPE (25- 90%), mortality 70% (higher if neurological symptoms are present of following CsA or tacrolimus use, 120days following HSCT)

Current Anaesthesia & Critical Care (2008) 19, 80–90

# Marrow infusion toxicity

- DMSO (dimethyl sulphoxide)
  - Cardiotoxicity: Bradyarrhythmias, CHF, cardiac arrest
  - ARF, ATN
- Mx: Hydration/ alkaline diuresis

# Tumour Lysis Syndrome

- ↑Urate/ K/ PO4
- ↓Calcium

- → Acute renal failure

- Mx: Hydration, renal support, forced alkaline diuresis, allopurinol prophylaxis, rasburicase

# Haemorrhagic cystitis

- Incidence 25% post HSCT
- Damage to urothelium due to chemo, viral infection or radiation
- Risk:
  - cyclophosphamide/bulsulphan
  - Virus: adenovirus, BK and CMV viruses
- Mx:
  - Mesna with CTX, forced alkaline diuresis, cystoscopy for bladder irrigation for clot

Current Anaesthesia & Critical Care (2008) 19, 80–90

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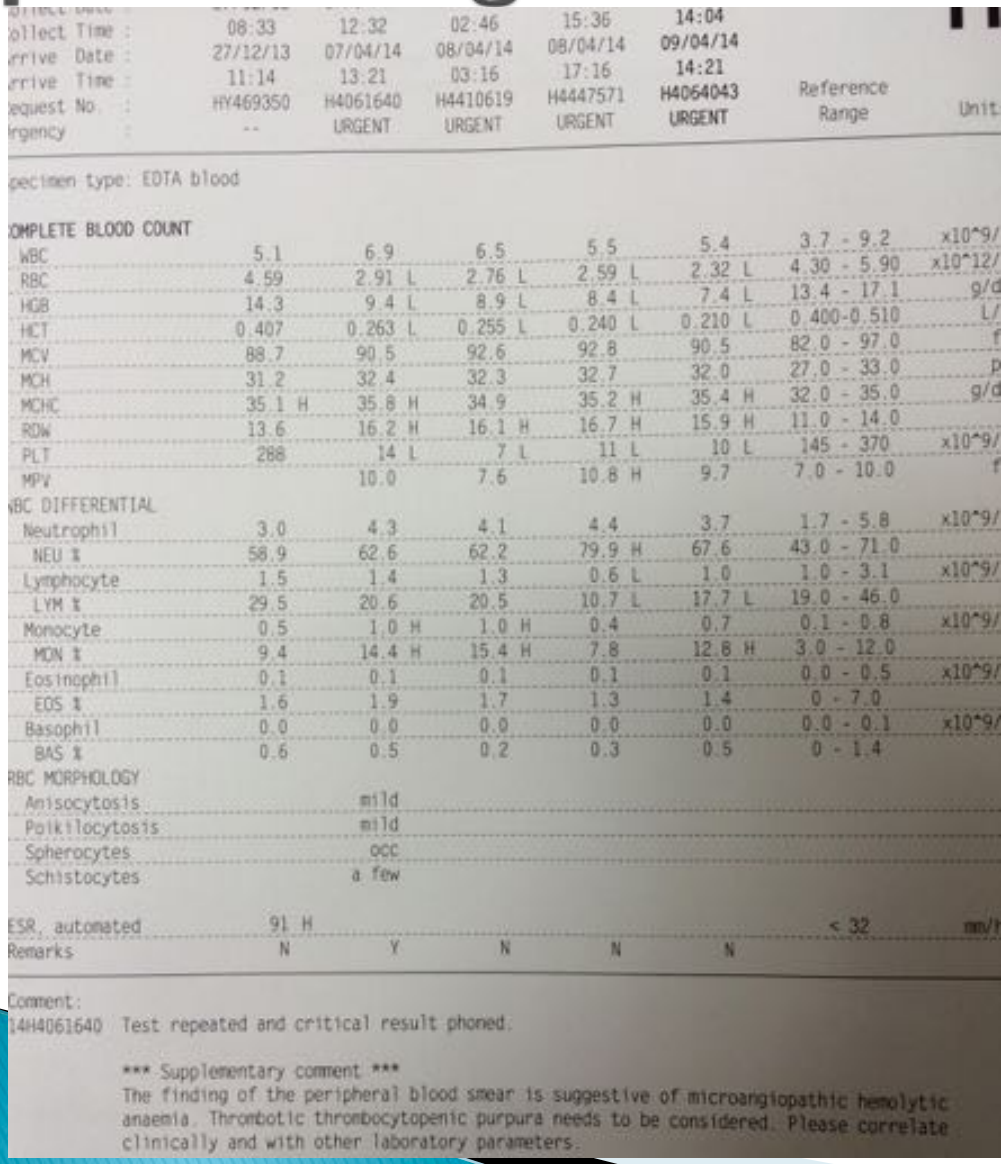
# Case: Elderly thrombocytopenia presenting with bleeding



| | 08:33 | 12:32 | 02:46 | 15:36 | 14:04 | | |
|---|---|---|---|---|---|---|---|
| Collect Time : | 27/12/13 | 07/04/14 | 08/04/14 | 08/04/14 | 09/04/14 | | |
| Arrive Date : | 11:14 | 13:21 | 03:16 | 17:16 | 14:21 | | |
| Arrive Time : | HY469350 | H4061640 | H4410619 | H4447571 | H4064043 | Reference | |
| Request No : | -- | URGENT | URGENT | URGENT | URGENT | Range | Unit |
| Urgency : | | | | | | | |
| Specimen type: EDTA blood | | | | | | | |
| COMPLETE BLOOD COUNT | | | | | | | |
| WBC | 5.1 | 6.9 | 6.5 | 5.5 | 5.4 | 3.7 - 9.2 | x10^9/ |
| RBC | 4.59 | 2.91 L | 2.76 L | 2.59 L | 2.32 L | 4.30 - 5.90 | x10^12/ |
| HGB | 14.3 | 9.4 L | 8.9 L | 8.4 L | 7.4 L | 13.4 - 17.1 | g/d |
| HCT | 0.407 | 0.263 L | 0.255 L | 0.240 L | 0.210 L | 0.400-0.510 | L/ |
| MCV | 88.7 | 90.5 | 92.6 | 92.8 | 90.5 | 82.0 - 97.0 | f |
| MCH | 31.2 | 32.4 | 32.3 | 32.7 | 32.0 | 27.0 - 33.0 | p |
| MCHC | 35.1 H | 35.8 H | 34.9 | 35.2 H | 35.4 H | 32.0 - 35.0 | g/d |
| RDW | 13.6 | 16.2 H | 16.1 H | 16.7 H | 15.9 H | 11.0 - 14.0 | |
| PLT | 288 | 14 L | 7 L | 11 L | 10 L | 145 - 370 | x10^9/ |
| MPV | | 10.0 | 7.6 | 10.8 H | 9.7 | 7.0 - 10.0 | f |
| WBC DIFFERENTIAL | | | | | | | |
| Neutrophil | 3.0 | 4.3 | 4.1 | 4.4 | 3.7 | 1.7 - 5.8 | x10^9/ |
| NEU % | 58.9 | 62.6 | 62.2 | 79.9 H | 67.6 | 43.0 - 71.0 | |
| Lymphocyte | 1.5 | 1.4 | 1.3 | 0.6 L | 1.0 | 1.0 - 3.1 | x10^9/ |
| LYM % | 29.5 | 20.6 | 20.5 | 10.7 L | 17.7 L | 19.0 - 46.0 | |
| Monocyte | 0.5 | 1.0 H | 1.0 H | 0.4 | 0.7 | 0.1 - 0.8 | x10^9/ |
| MON % | 9.4 | 14.4 H | 15.4 H | 7.8 | 12.8 H | 3.0 - 12.0 | |
| Eosinophil | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 | 0.0 - 0.5 | x10^9/ |
| EOS % | 1.6 | 1.9 | 1.7 | 1.3 | 1.4 | 0 - 7.0 | |
| Basophil | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 - 0.1 | x10^9/ |
| BAS % | 0.6 | 0.5 | 0.2 | 0.3 | 0.5 | 0 - 1.4 | |
| RBC MORPHOLOGY | | | | | | | |
| Anisocytosis | | mild | | | | | |
| Poikilocytosis | | mild | | | | | |
| Spherocytes | | occ | | | | | |
| Schistocytes | | a few | | | | | |
| ESR, automated | 91 H | | | | | < 32 | mm/ |
| Remarks | N | Y | N | N | N | | |

Comment:
14H4061640 Test repeated and critical result phoned.

*** Supplementary comment ***
The finding of the peripheral blood smear is suggestive of microangiopathic hemolytic anaemia. Thrombotic thrombocytopenic purpura needs to be considered. Please correlate clinically and with other laboratory parameters.

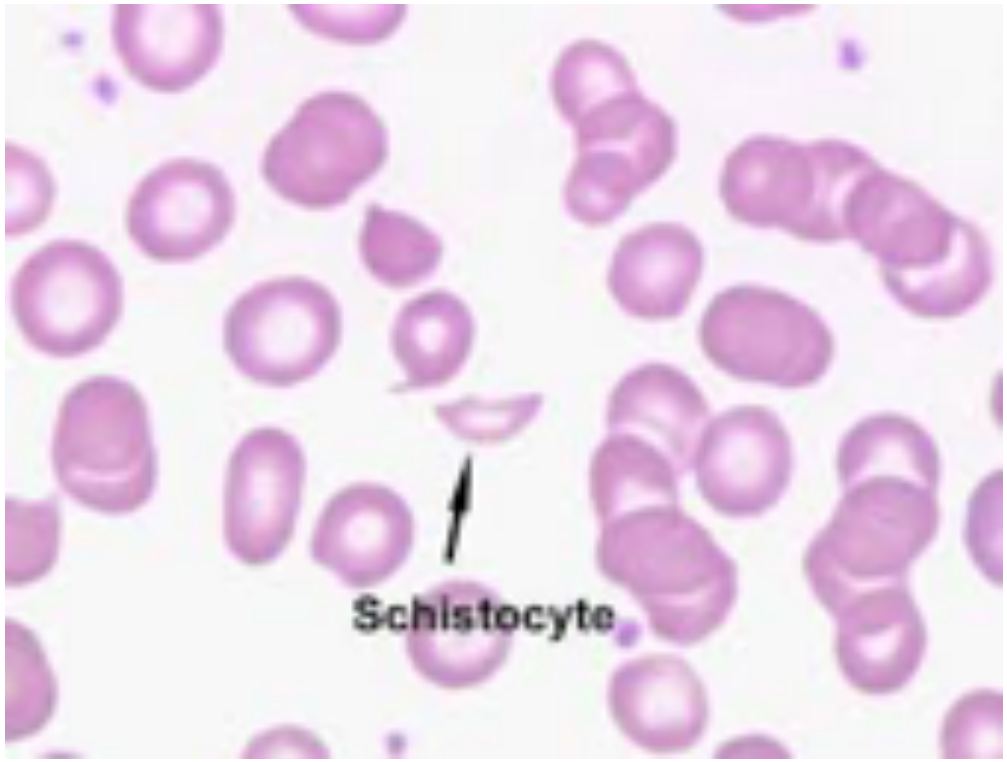
Good past health

AED : due to petechia

-GCS 15/15
-RFT normal
-Low grade fever on admission, no chest infection S/S

Pentriad:
Neurological symptoms
Renal failure
**Fever**
**MAHA**
**↓ Platelet**

# Schistocytes: MAHA



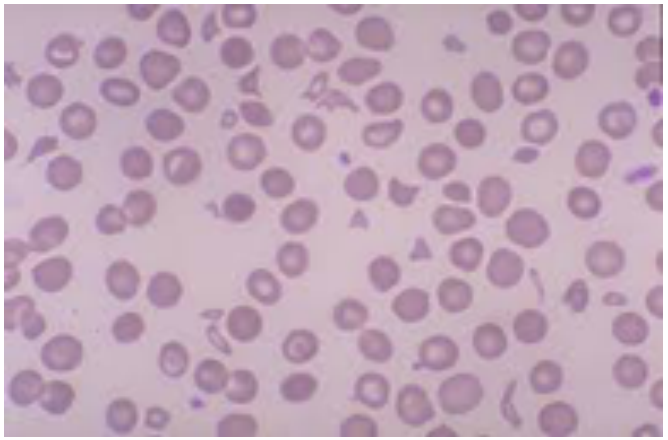



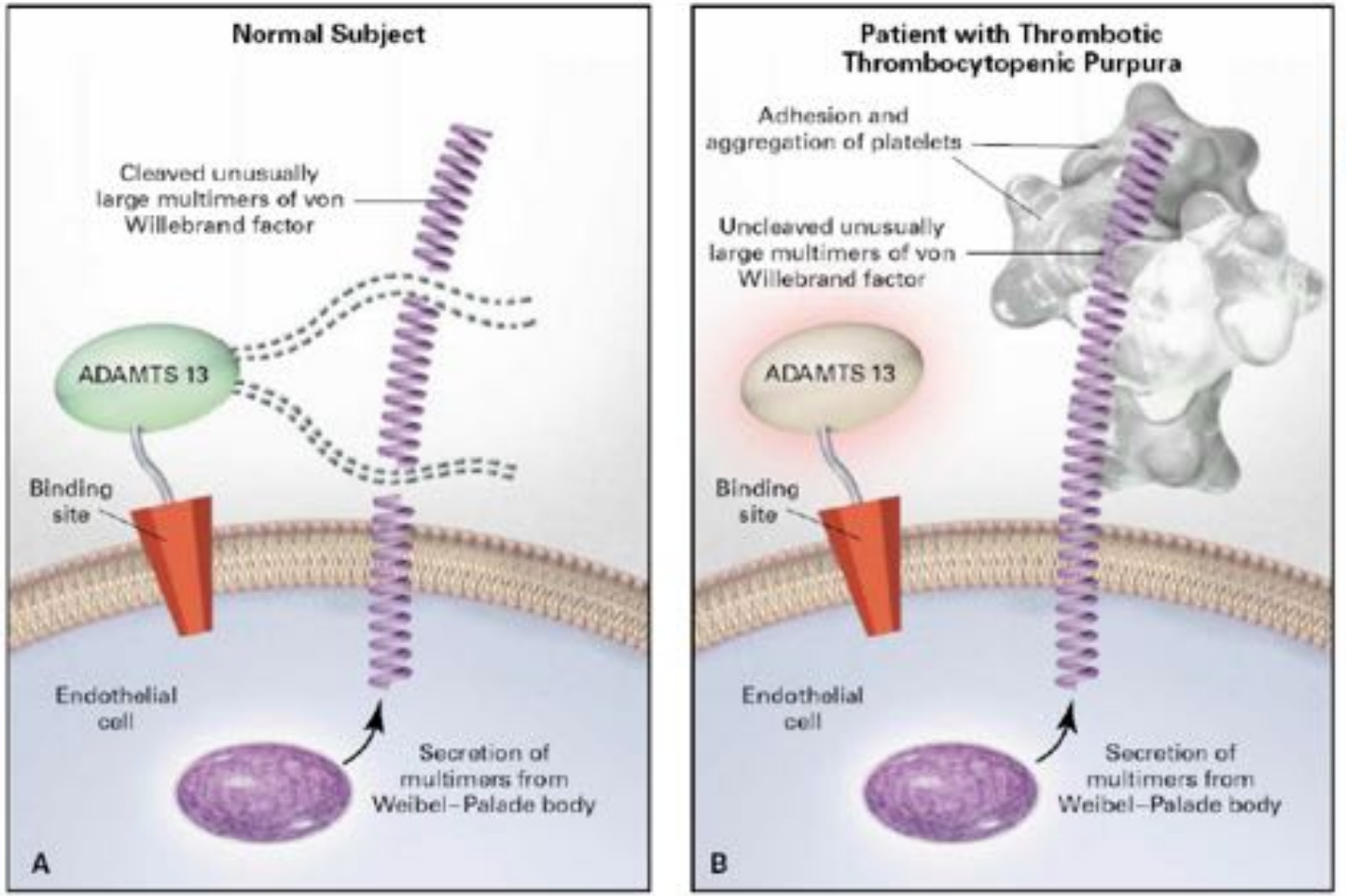
**Table I.** Differential diagnosis of thrombocytopenia and microangiopathic haemolytic anaemia.

| |
|---|
| Autoimmune haemolysis/Evans syndrome |
| Disseminated intravascular coagulation |
| Pregnancy-associated e.g. HELLP (haemolysis, elevated liver enzymes and low platelets), eclampsia, haemolytic uraemic syndrome |
| Drugs eg quinine, simvastatin, interferon, Calcineurin inhibitors |
| Malignant hypertension |
| Infections, typically viral (cytomegalovirus, adenovirus, herpes simplex virus) or severe bacterial (meningococcus, pneumococcus), fungal |
| Autoimmune disease (lupus nephritis, acute scleroderma) |
| Vasculitis |
| Haemolytic uraemic syndrome (diarrhoea positive/negative) |
| Malignancy |
| Catastrophic antiphospholipid syndrome |

•AML M6

BCSH guidelines 2012

# TTP: pathology




Joel L. Moake NEJM 2002

# Confirmatory test

- ADAMTS13 Antigen
- ADAMTS13 Antibody

# DDX: pregnancy associated MAHA

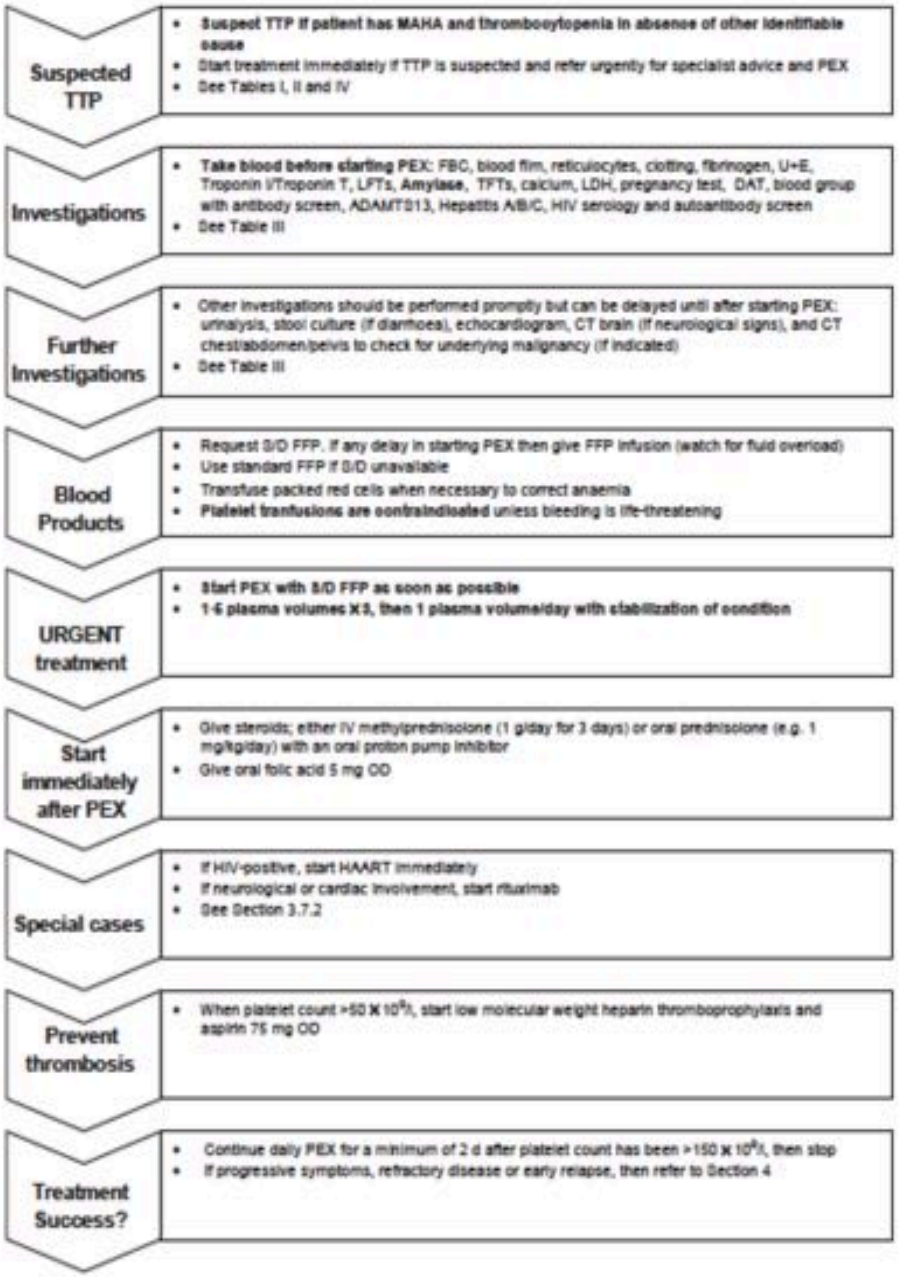
Table IV. Typical features in pregnancy-associated microangiopathies.

| | MAHA | Thrombo cytopenia | Coagulo pathy | HBP | Abdominal symptoms | Renal Impairment | Neurological symptoms |
|---|---|---|---|---|---|---|---|
| PET | + | + | ± | +++ | ± | ± | ++ |
| HELLP | + | ++ | ± | + | +++ | + | ± |
| TTP | ++ | +++ | – | ± | + | ++ | +++ |
| HUS | + | ++ | ± | ++ | + | +++ | ± |
| AFLP | ± | + | ++++ | + | +++ | ++ | + |
| SLE | + | + | ± | + | ± | ++ | + |
| APLS | + | ++ | ± | ± | ± | ± | ± |

PET, pre-eclampsia; HELLP, haemolysis, elevated liver enzymes and low platelets; TTP, thrombotic thrombocytopenia purpura; HUS, haemolytic-uraemic syndrome; AFLP, acute fatty liver of pregnancy; SLE, systemic lupus erythematosus; APLS, Antiphospholipid syndrome (catastrophic), MAHA, microangiopathic haemolytic anaemia; HBP, hypertension.

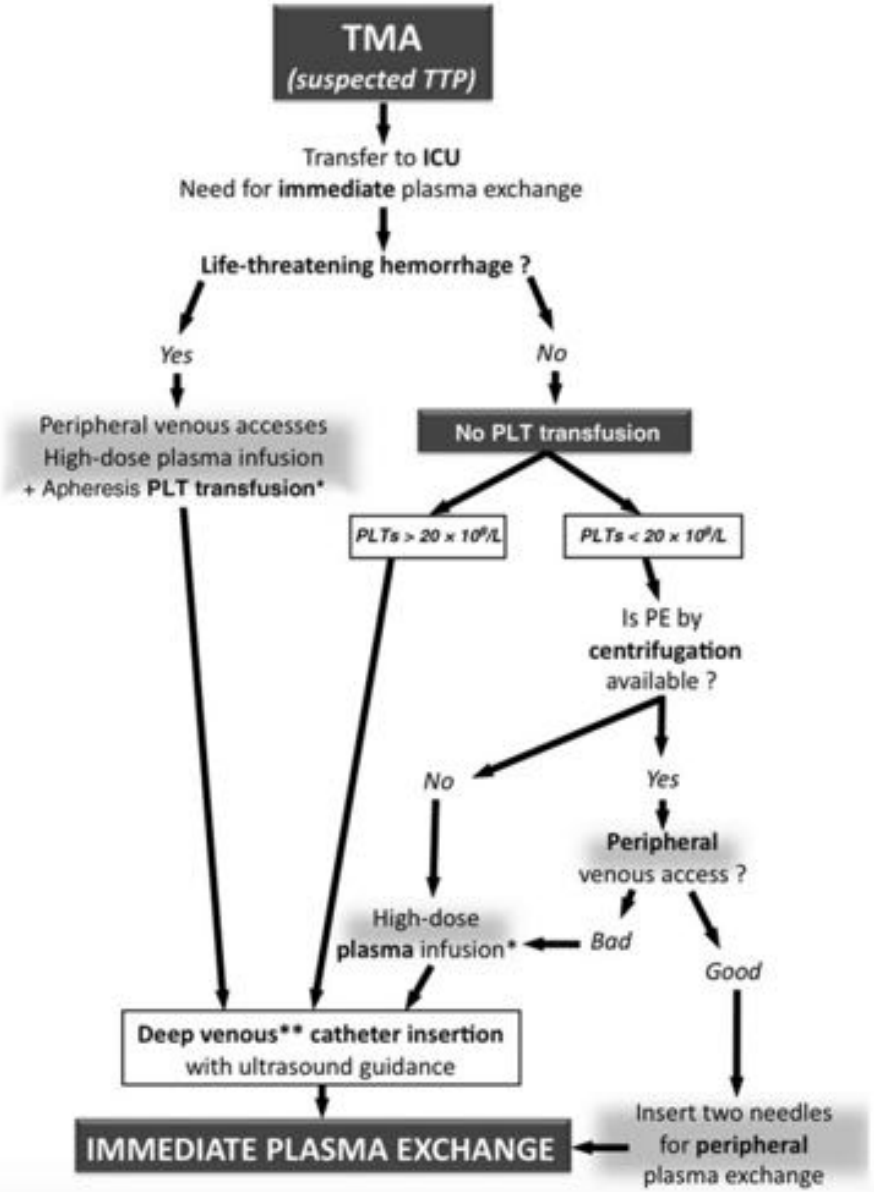
BCSH guidelines 2012

# Mx : Medical emergency TTP




BCSH guidelines 2012

# Venous access for TPE in TTP




Volume 00, Month 2015 TRANSFUSION

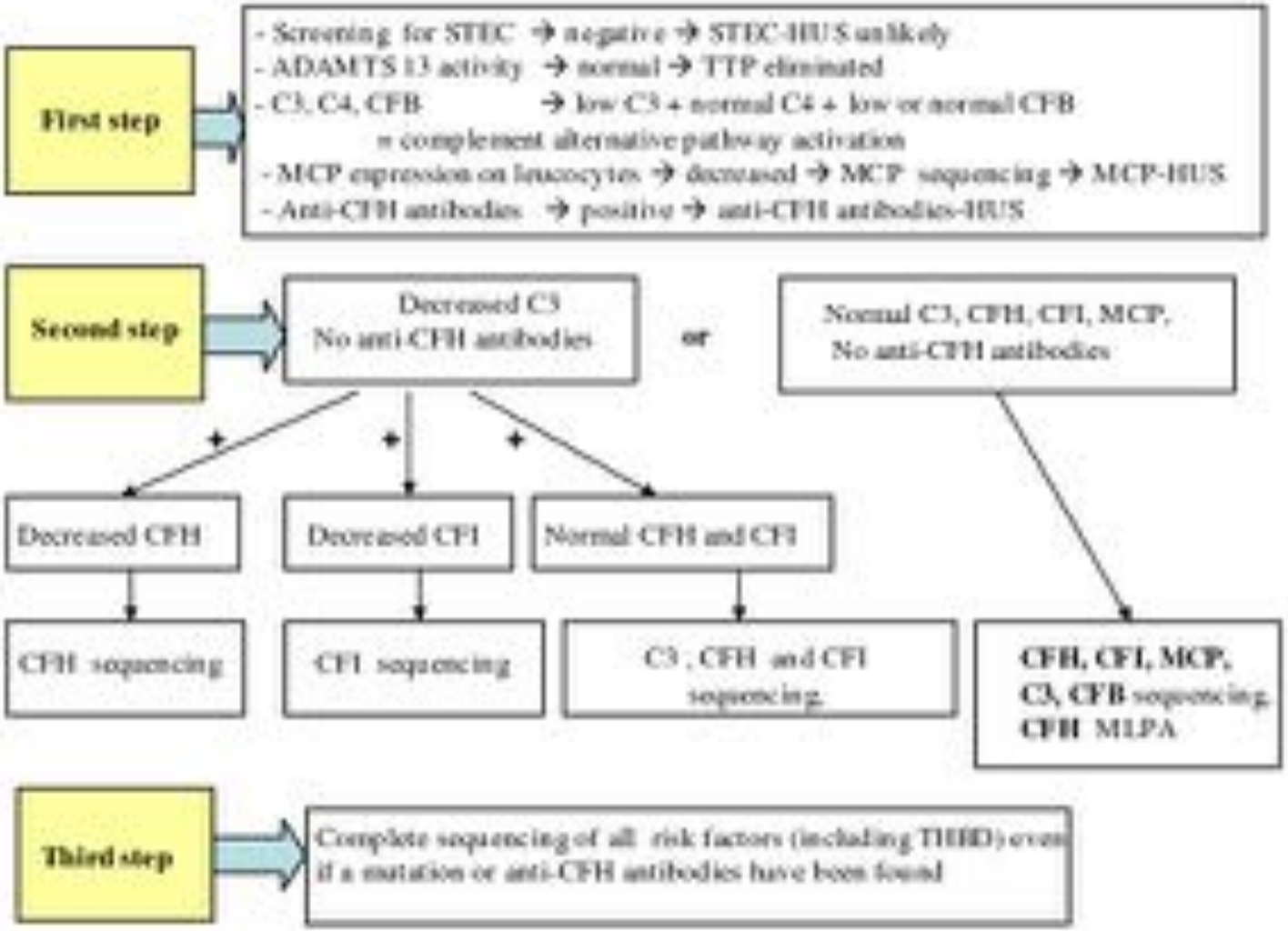
# HUS

**Table 1** Classification and treatment of the different forms of HUS

| Disease | Causes | Treatment |
|---|---|---|
| D+ HUS | Stx-producing Escherichia coli | Support |
| | Shigella dysenteriae type 1 | Support and antibiotics |
| Non-Stx HUS (sporadic) | Bacterium (Streptococcus pneumoniae) | Antibiotics and plasma |
| | Virus (HIV) | Plasma |
| | Drugs (antineoplastic, antiplatelet, immunosuppressive drugs) | Drug interruption and plasma |
| | Pregnancy | Delivery, plasma |
| | Post-partum | Plasma |
| | Systemic diseases | |
| | Lupus | Steroids and plasma |
| | Scleroderma | Blood pressure control |
| | Antiphospholipid syndrome | Oral anticoagulant agents |
| | Idiopathic | Plasma |
| | Genetic (CFH, MCP, CFI) | Plasma |
| Familial | Genetic (CFH, MCP, CFI), plasma | Plasma |

J. Bras. Nefrol. vol.32 no.3 São Paulo July/Sept. 2010

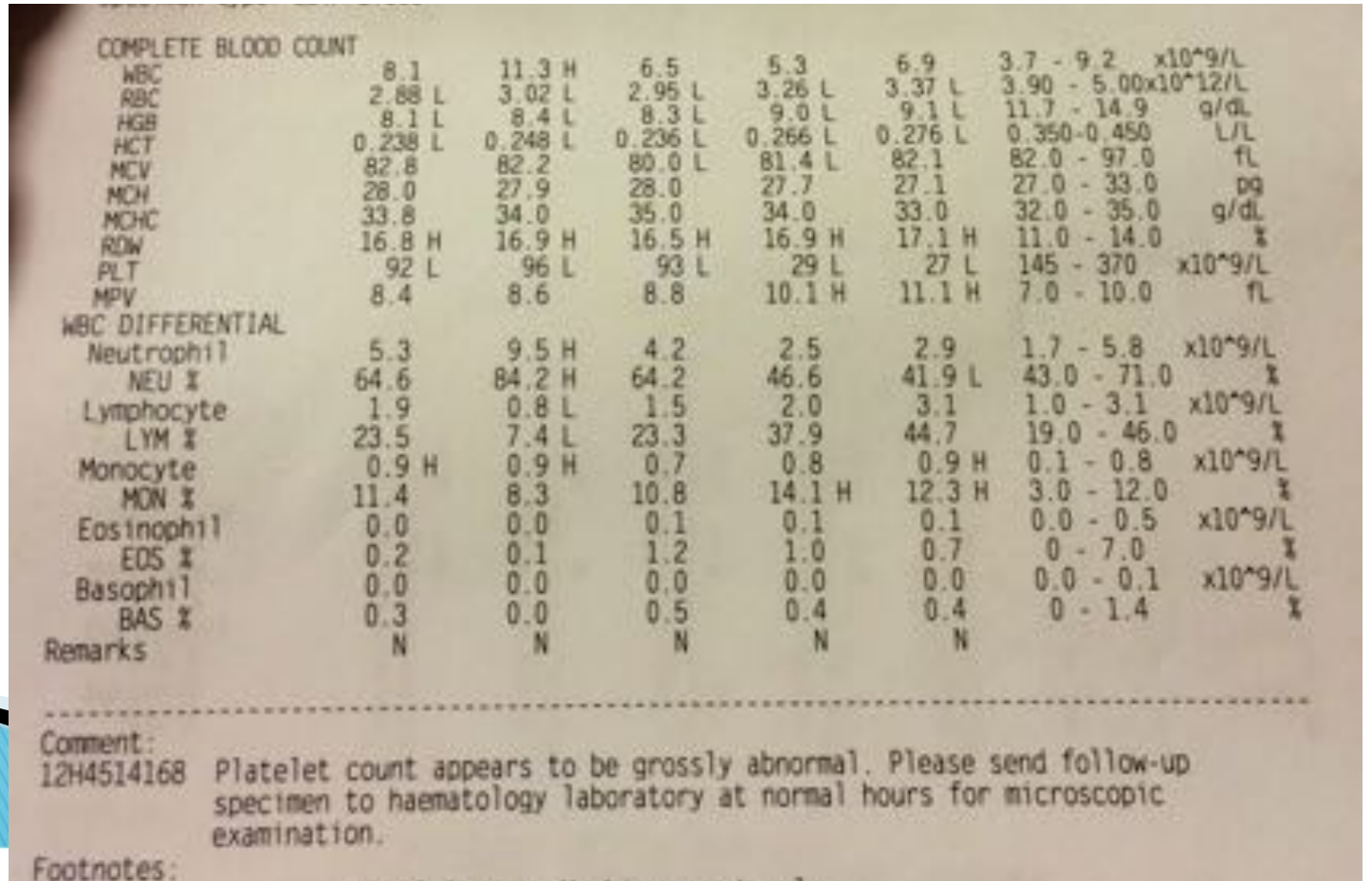
# Dx approach: HUS



# Case : Thrombocytopenia after anticoagulation

- History of MM post ABMT, disease static
- Acute limb ischaemic requiring AKA and heparin infusion 21/3/2012
- Drop of platelet count 2/4/2012 (13 days)
- LA/ Anticardiolipin Abs negative

# Platelet count drop after operation



COMPLETE BLOOD COUNT

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| WBC | 8.1 | 11.3 H | 6.5 | 5.3 | 6.9 | 3.7 - 9.2 | x10^9/L |
| RBC | 2.88 L | 3.02 L | 2.95 L | 3.26 L | 3.37 L | 3.90 - 5.00 | x10^12/L |
| HGB | 8.1 L | 8.4 L | 8.3 L | 9.0 L | 9.1 L | 11.7 - 14.9 | g/dL |
| HCT | 0.238 L | 0.248 L | 0.236 L | 0.266 L | 0.276 L | 0.350-0.450 | L/L |
| MCV | 82.8 | 82.2 | 80.0 L | 81.4 L | 82.1 | 82.0 - 97.0 | fL |
| MCH | 28.0 | 27.9 | 28.0 | 27.7 | 27.1 | 27.0 - 33.0 | pg |
| MCHC | 33.8 | 34.0 | 35.0 | 34.0 | 33.0 | 32.0 - 35.0 | g/dL |
| RDW | 16.8 H | 16.9 H | 16.5 H | 16.9 H | 17.1 H | 11.0 - 14.0 | % |
| PLT | 92 L | 96 L | 93 L | 29 L | 27 L | 145 - 370 | x10^9/L |
| MPV | 8.4 | 8.6 | 8.8 | 10.1 H | 11.1 H | 7.0 - 10.0 | fL |
| WBC DIFFERENTIAL | | | | | | | |
| Neutrophil | 5.3 | 9.5 H | 4.2 | 2.5 | 2.9 | 1.7 - 5.8 | x10^9/L |
| NEU % | 64.6 | 84.2 H | 64.2 | 46.6 | 41.9 L | 43.0 - 71.0 | % |
| Lymphocyte | 1.9 | 0.8 L | 1.5 | 2.0 | 3.1 | 1.0 - 3.1 | x10^9/L |
| LYM % | 23.5 | 7.4 L | 23.3 | 37.9 | 44.7 | 19.0 - 46.0 | % |
| Monocyte | 0.9 H | 0.9 H | 0.7 | 0.8 | 0.9 H | 0.1 - 0.8 | x10^9/L |
| MON % | 11.4 | 8.3 | 10.8 | 14.1 H | 12.3 H | 3.0 - 12.0 | % |
| Eosinophil | 0.0 | 0.0 | 0.1 | 0.1 | 0.1 | 0.0 - 0.5 | x10^9/L |
| EOS % | 0.2 | 0.1 | 1.2 | 1.0 | 0.7 | 0 - 7.0 | % |
| Basophil | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 - 0.1 | x10^9/L |
| BAS % | 0.3 | 0.0 | 0.5 | 0.4 | 0.4 | 0 - 1.4 | % |
| Remarks | N | N | N | N | N | | |

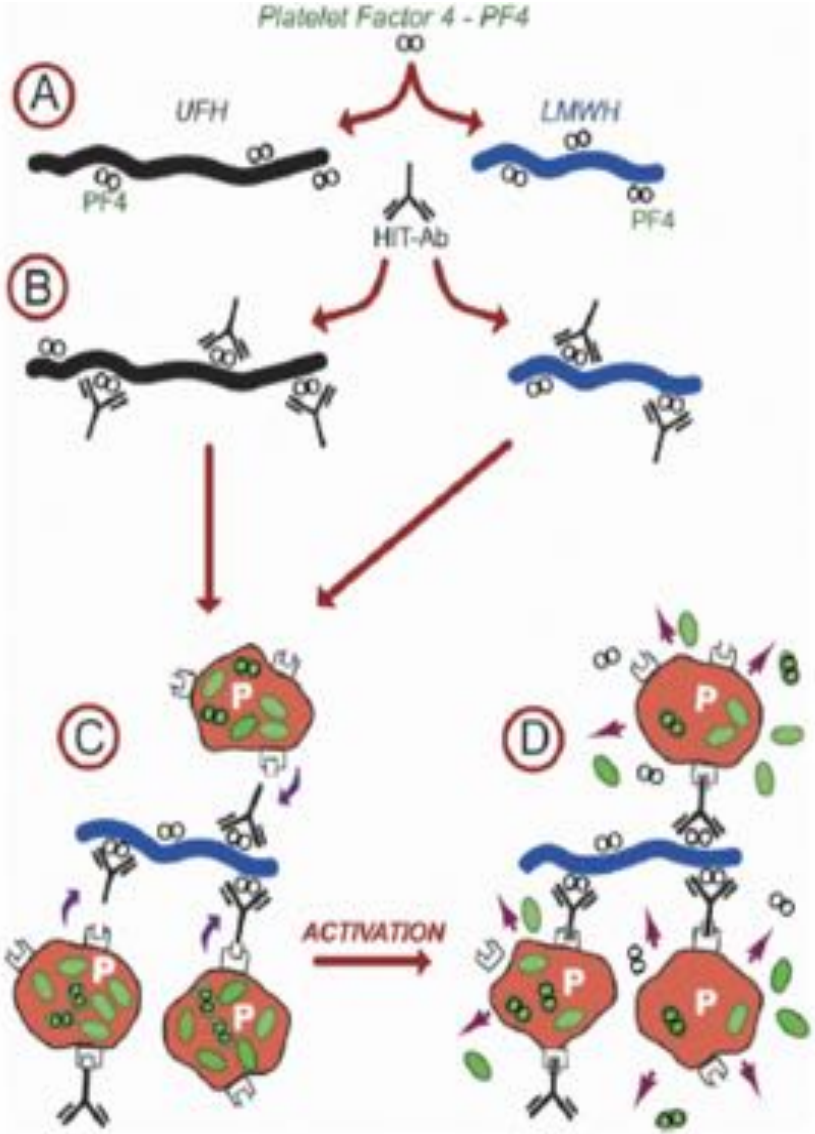
Comment:
12H4514168 Platelet count appears to be grossly abnormal. Please send follow-up specimen to haematology laboratory at normal hours for microscopic examination.

Footnotes:

# DDX?

- DIC/ sepsis
- Marrow failure
- TTP
- HIT
- Others ?

# Dx of HIT: anti-hepatin-PF4 Ab (ELIZA)




J Vasc Surg. 2012 Feb;55(2):562-70

# 4T clinical scoring system for HIT

**Table I.** The 4T scoring system for the diagnosis of heparin-induced thrombocytopenia[57]

| *Variable*[a] | *0* | *1* | *2* |
|---|---|---|---|
| Thrombocytopenia | <30% fall | 30%-50% fall | >50% fall |
| Timing of platelet count fall | Within 4 days after exposure without recent exposure | After day 10 or missing documentation or within 4 days after exposure with recent exposure 30-100 days ago | Between 5 and 10 days of heparin or within 4 days after exposure with recent exposure in the previous 30 days |
| Thrombosis | None | Progressive or recurrent thrombosis, erythematous skin lesions, suspected thrombosis | New confirmed thrombosis, skin necrosis, acute systemic response to IV UFH bolus |
| Other causes of thrombocytopenia | Definite other cause | Possible other cause | No other cause |

*IV*, Intravenous; *UFH*, unfractionated heparin.

[a]Points assigned in each of four categories are totaled. The pretest probability of heparin-induced thrombocytopenia is determined by the total points as follows: high, 6 to 8 points; intermediate, 4 to 5 points; and low, 0 to 3 points.

J Vasc Surg. 2012 Feb;55(2):562-70

# Mx: HIT

**Table II.** Alternative anticoagulants for heparin-induced thrombocytopenia management

| *Drug* | *Dose* | *Half-life* | *Clearance* | *Monitoring* | *Therapeutic range* | *Cost/day* | *Adverse effects* |
|---|---|---|---|---|---|---|---|
| Lepirudin (IV) | Bolus 0.2-0.4 mg/kg; then 0.1 mg/kg/h | 80 min | Renal | aPTT | 1.5-2.0 × baseline | $700 | Bleeding,* antilepirudin antibodies, anaphylactic reactions |
| Argatroban (IV) | 2 μg/kg/min | 45 min | Hepatic | aPTT | 1.5-2.0 × baseline | $600 | Bleeding* |
| Bivalirudin (IV) | 0.15-0.2 mg/kg/h | 30 min | Proteolysis, renal | aPTT | 1.5-2.0 × baseline | $670 | Bleeding* |
| Danaparoid (IV) | Bolus 2500 U; then 150-200 U/h | 24 h | Renal | Anti Xa | 0.5-0.8 U/mL | $ 74 | Bleeding,* cross-reactivity with anti-PF4/heparin antibodies |
| Fondaparinux (SC) | 5.0-7.5 mg | 20 h | Renal | . . . | . . . | $105 | Bleeding,* cross-reactivity with anti-PF4/heparin antibodies |

*aPTT*, Activated partial thromboplastin time; *IV*, intravenous; *PF4*, platelet factor 4; *SC*, subcutaneous.
*In patients without heparin-induced thrombocytopenia, only lepirudin increases the risk of bleeding vs heparin.

J Vasc Surg. 2012 Feb;55(2):562-70

# Topics

- Neutropenic fever
- Treatment aim for hematology patients
- Post HSCT complications
- Thrombocytopenia for ICU care
- Management of uraemic bleeding
- Prophylactic/ therapeutic platelet transfusion in hematological cancer patients

# Case: normal platelet count/ clotting profile but bleeding tendency

- Acquired
  - ESRF with bleeding from wound
  - Patients on anti-platelet

- Congenital
  - Paediatrics patients with congenital platelet dysfunction
    - Glanzmann's thrombasthenia (GT)
    - Bernard-Soulier syndrome (BSS)
    - Storage pool disease,
    - Thromboxane A2 receptor defect

# Uremic bleeding: treatment

**Table 6** Summary of relative effects of different treatment options in uremic bleeding.

| Treatment option | Prevents uremic platelet dysfunction | Effective for active bleeding | Useful in males and females | Improves platelet adhesion | Improves platelet aggregation | Increases platelet size or number | Reduces bleeding time | Normalizes bleeding time |
|---|---|---|---|---|---|---|---|---|
| Dialysis | + | – | + | – | + | + | ++ | + |
| Recombinant human EPO | + | +/– | + | + | + | + | ++ | + |
| Cryoprecipitate | – | ++ | + | – | – | – | ++ | + |
| Desmopressin | – | +++ | + | – | +/– | – | +++ | ++ |
| Estrogen intravenous | – | + | + | – | + | – | ++ | + |
| Estrogen oral | – | + | + | – | + | – | + | + |
| Estrogen transdermal | – | + | + | – | – | – | + | – |

Abbreviation: EPO, erythropoietin.

Nature Clinical Practice Nephrology (2007) **3, 138-153**

# Uraemic bleeding: approach

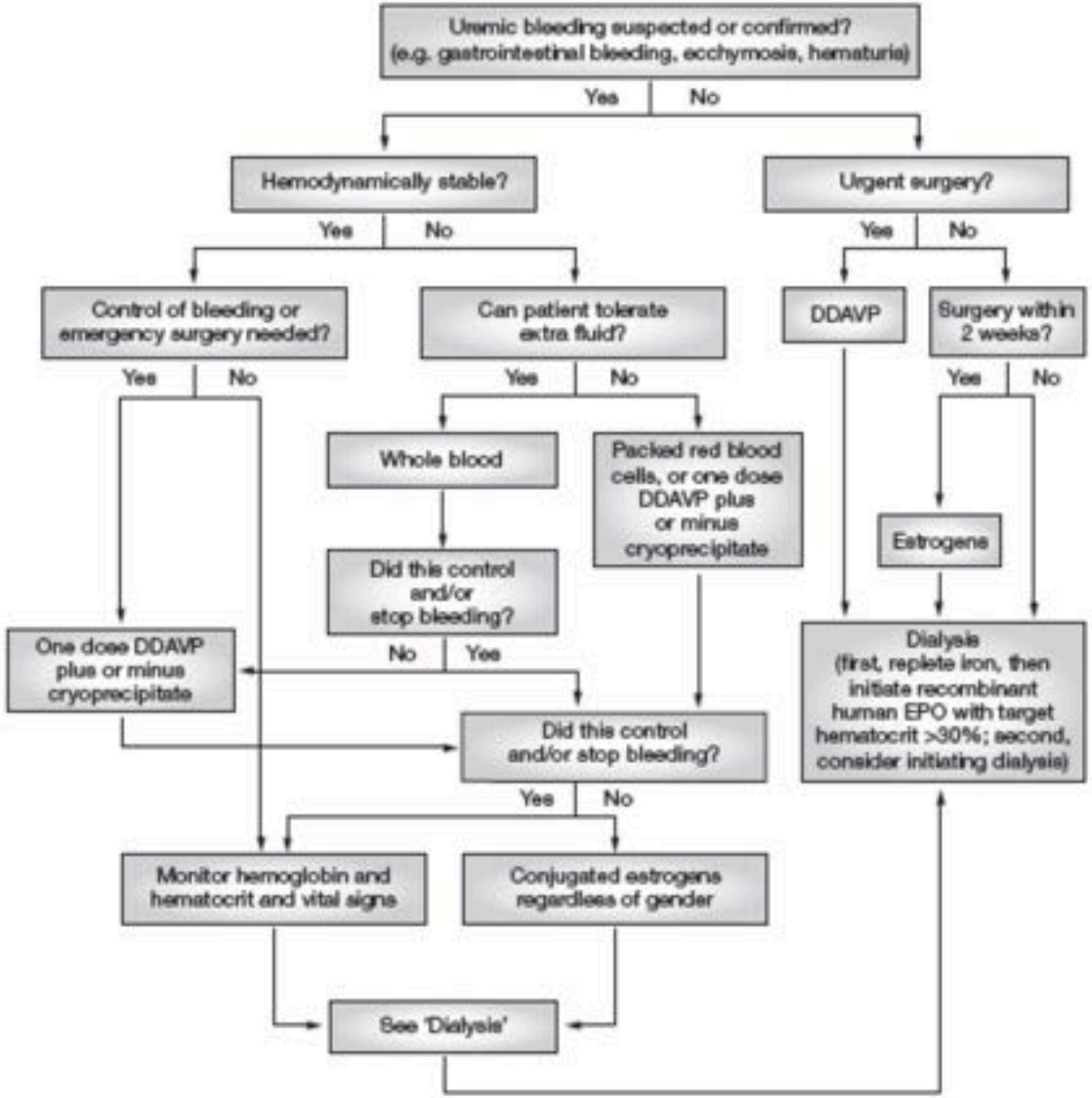



**Figure 1** Algorithm for the management of uremic platelet dysfunction. If at any stage in the algorithm the patient

Nature Clinical Practice Nephrology (2007) 3, 138-153

# Topics

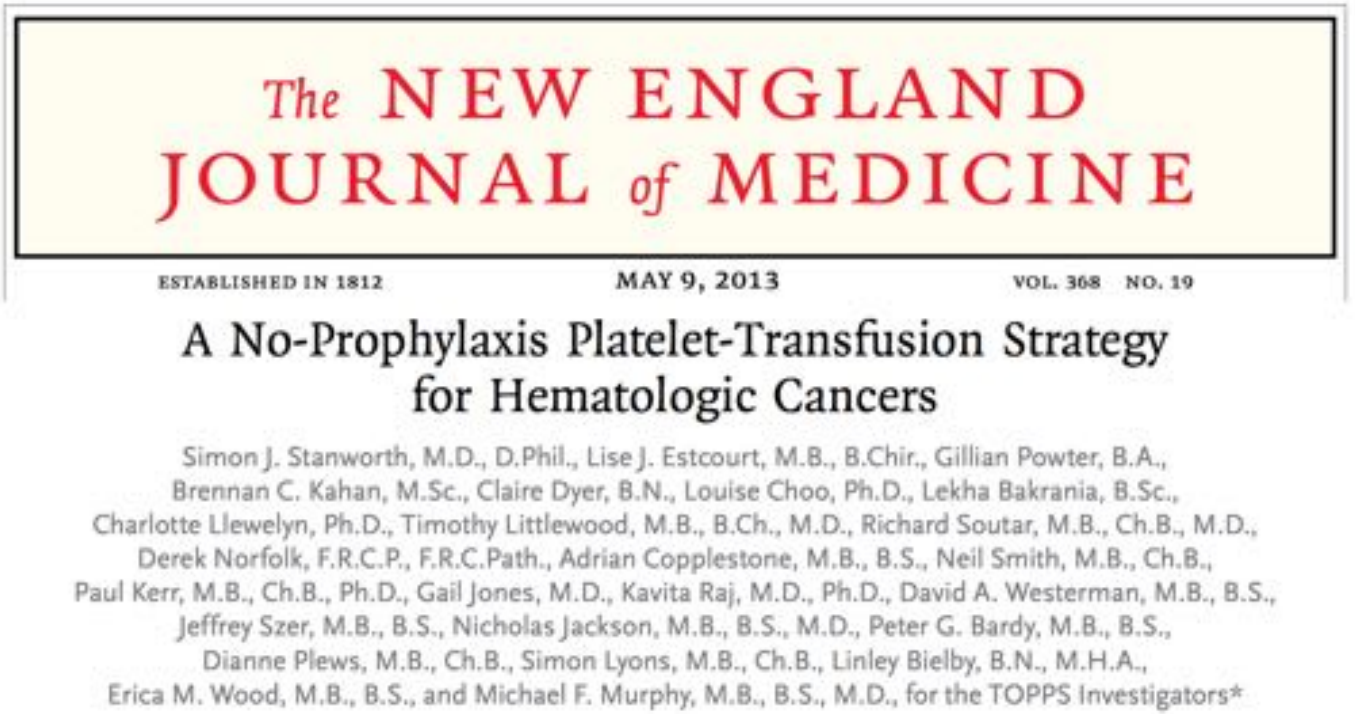
- Neutropenic fever
- Treatment aim for hematology patients
- Post HSCT complications
- Thrombocytopenia for ICU care
- Management of uraemic bleeding
- Prophylactic/ therapeutic platelet transfusion in hematological cancer patients

# Case: thrombocytopenia in marrow failure

- ? Threshold for prophylactic platelet transfusion

- Cochrane database 2012
  - No evidence to suggest a change from threshold $10 \times 10^{9}$/L to $20 \times 10^{9}$/L

Cochrane Database Syst Rev. 2012 May.



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 9, 2013 VOL. 368 NO. 19

# A No-Prophylaxis Platelet-Transfusion Strategy for Hematologic Cancers

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- TOPPS: UK/ Australia trial
- Question:

  Is a non-prophylactic platelet transfusion policy non-inferior to (no worse than) prophylaxis for hematological cancer patients?

NEJM 2013: 368;19

**Table 2. Primary and Secondary Bleeding Outcomes.***

| Outcome | No Prophylaxis (N=301) | Prophylaxis (N=299) | No Prophylaxis vs. Prophylaxis | P Value |
|---|---|---|---|---|
| **Primary end point** | | | | |
| WHO grade 2, 3, or 4 bleeding — no. (%) | 151 (50) | 128 (43) | 8.4 (1.7 to 15.2)†‡ | 0.06§ |
| **Secondary end points** | | | | |
| Highest grade of bleeding — no. (%) | | | | |
| None or 1 | 149 (50) | 170 (57) | | |
| 2 | 145 (48) | 127 (43) | | |
| 3 | 4 (1) | 1 (<1) | | |
| 4 | 2 (1) | 0 | | |
| No. of days from randomization to first episode of grade 2, 3, or 4 bleeding | 17.2±12.8 | 19.5±12.6 | 1.30 (1.04 to 1.64)¶ | 0.02‖ |
| Grade 3 or 4 bleeding — no. (%) | 6 (2) | 1 (<1) | 6.05 (0.73 to 279.72)** | 0.13‖ |
| No. of days with grade 2, 3, or 4 bleeding†† | 1.7±2.9 | 1.2±2.0 | 1.52 (1.14 to 2.03)‡‡ | 0.004‖ |
| Bleeding events of grade 2, 3, or 4 according to treatment and type of cancer — no./total no. (%) | | | | |
| Treatment | | | | |
| Autologous stem-cell transplantation | 99/210 (47) | 95/210 (45) | 2.3 (−5.7 to 10.3)† | |
| Chemotherapy | 52/90 (58) | 33/88 (38) | 20.0 (7.9 to 32.2)† | 0.04§§ |
| Type of cancer | | | | |
| Acute myeloid leukemia or acute lymphoid leukemia | 37/60 (62) | 21/56 (38) | 24.2 (9.6 to 28.9)† | |
| Lymphoma or myeloma | 107/226 (47) | 100/227 (44) | 3.3 (−4.4 to 11.0)† | |
| Chronic myeloid leukemia or other cancer | 7/14 (50) | 7/15 (47) | 3.3 (−27.2 to 33.9)† | 0.10§§ |

NEJM 2013: 368;19

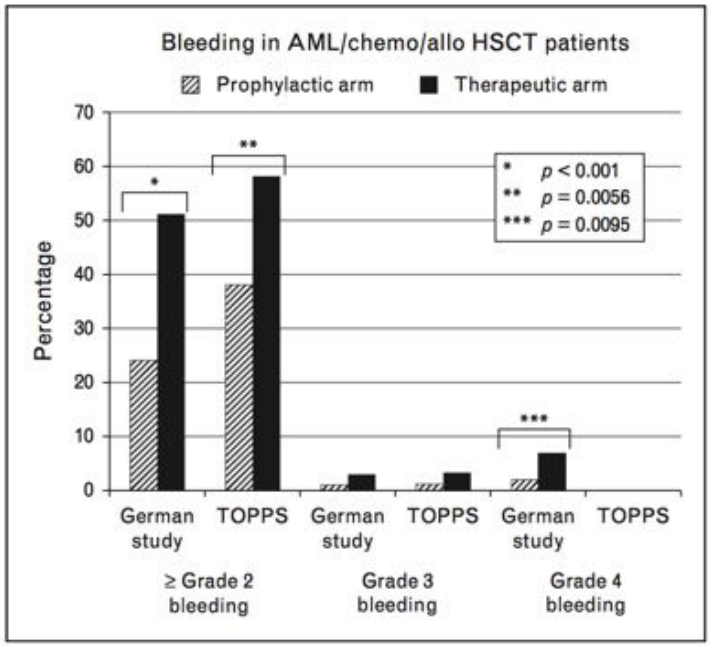
# Study Outcome

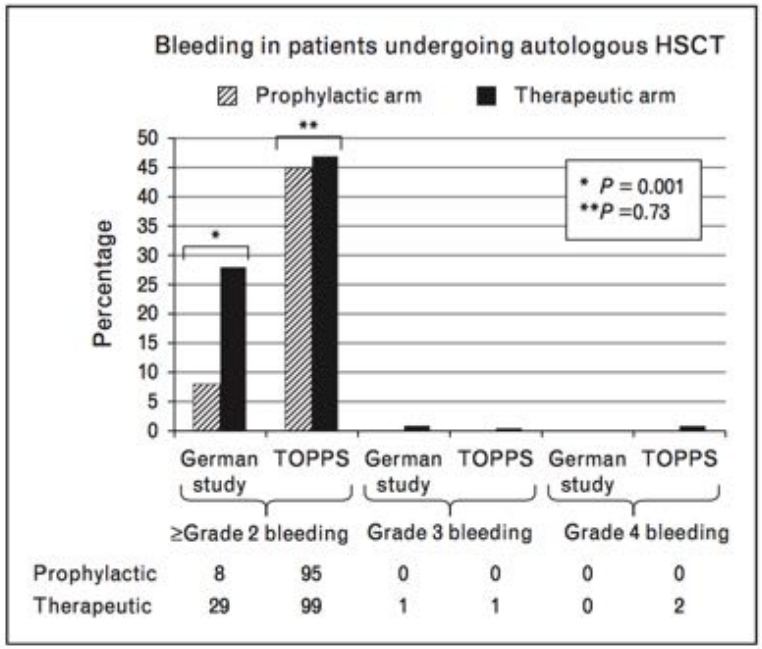
- WHO grade 2-4 bleeding
  - Non prophylaxis: 50% (151/300)
  - Prophylaxis: 43%  (128/ 298)
- Non inferiority trials:
  - 90% CI: 1.7 to 15.2,  p=0.06
  - Adjusted difference in proportion 8.5%
  - Study did not show a prophylaxis policy was non-inferior to (no worse than) prophylaxis
- ➔Non-prophylaxis group had more days with bleeding and a shorter time to the first bleeding episode than did patients in the prophylaxis group.
- ➔Platelet use was markedly reduced in the no-prophylaxis group.

NEJM 2013: 368;19

# Meta-analysis: German/ UK-Australian Study

- We <u>should</u> continue to receive prophylactic platelet transfusions to prevent high-grade bleeding.
- Stable ASCT patients : a lower risk of thrombocytopenia-related bleeding and are candidates for therapeutic-only platelet transfusions in expert centers with careful monitoring.




Zeller at al. Curr Opin Hematology Nov 2014

# Summary

- Busy ward: current platelet transfusion threshold applies
- Patients with hematological cancers should receive prophylactic platelet transfusion

# Conclusion
# Haematolgical malignancy

- Improvement in treatment for leukaemia,  lymphoma and myeloma
- Life-saving if supportive care is provided during period of having post-chemotherapy complications till marrow recovery
- Highly immunocompromised
- Management foci:
  - Not only eradication of malignant cells
  - Infection
  - Bleeding
  - Prevention of thrombosis
  - Emotional and family support for their high expectation of recovery