Transfusion: indications (RBC, platelets, granulocytes, plasma)

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Indications for the transfusion of erythrocytes
General rules

➢ only transfuse if the risk of not-transfusing > risk of the transfusion (risk-benefit)

➢ carrying out a transfusion is NOT only decided by a lab value, always evaluate the clinical condition of the patient

➢ there is no magic ‘transfusion threshold’
transfusing RBC without controlling tissue O2 demands, makes little clinical sense (fever, septic shock, convulsions …) → aggressive etiologic and haemodynamic treatment must be initiated.

O2 transport is determined by both cardiac output and the concentration of O2 in blood

\[ \text{DO}_2 = \text{CaO}_2 \times \text{CO} \]

\text{DO}_2 = \text{oxygen delivery to tissues}
\text{CaO}_2 = \text{amount of arterial O2}
\text{CO} = \text{cardiac output}
Trigger Hb concentration

- Hb \( \geq 10 \text{ g/dl} \) → rarely a transfusion is needed

- Hb 7-10 g/dl → low risk of hypoxic organ damage in most of the patients: « Why transfuse? ». Decision determined by clinical condition.

- Hb < 7 g/dl → substantial risk of hypoxic organ damage: « Why not transfuse? »

- Hb < 4.5 g/dl → life of the patient is in immediate danger.

Other factors

- duration of anemia (acute versus chronic)
- clinical evaluation: cardiovascular, pulmonary, cerebral status. Risk of volume overload?
- possibility of acute bleeding?
**TRICC-trial: transfusion requirement in critical care**

### Table 3. Complications That Occurred during the Patients’ Stays in the Intensive Care Unit.

<table>
<thead>
<tr>
<th>Complication*</th>
<th>Restrictive-Transfusion Strategy (N=418)</th>
<th>Liberal-Transfusion Strategy (N=420)</th>
<th>Absolute Difference between Groups</th>
<th>95% Confidence Interval†</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no. (%)</td>
<td>percent</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac</td>
<td>55 (13.2)</td>
<td>88 (21.0)</td>
<td>7.8</td>
<td>2.7 to 12.9</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>3 (0.7)</td>
<td>12 (2.9)</td>
<td>2.1</td>
<td>—</td>
<td>0.02</td>
</tr>
<tr>
<td>Pulmonary edema</td>
<td>22 (5.3)</td>
<td>45 (10.7)</td>
<td>5.5</td>
<td>1.8 to 9.1</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Angina</td>
<td>5 (1.2)</td>
<td>9 (2.1)</td>
<td>0.9</td>
<td>—</td>
<td>0.28</td>
</tr>
<tr>
<td>Cardiac arrest</td>
<td>29 (6.9)</td>
<td>33 (7.9)</td>
<td>0.9</td>
<td>-2.6 to 4.5</td>
<td>0.60</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>106 (25.4)</td>
<td>122 (29.0)</td>
<td>3.7</td>
<td>-2.3 to 9.7</td>
<td>0.22</td>
</tr>
<tr>
<td>ARDS</td>
<td>32 (7.7)</td>
<td>48 (11.4)</td>
<td>3.8</td>
<td>-0.2 to 7.8</td>
<td>0.06</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>87 (20.8)</td>
<td>86 (20.5)</td>
<td>-0.3</td>
<td>-5.8 to 5.1</td>
<td>0.92</td>
</tr>
<tr>
<td>Infectious</td>
<td>42 (10.0)</td>
<td>50 (11.9)</td>
<td>1.9</td>
<td>-2.4 to 6.1</td>
<td>0.38</td>
</tr>
<tr>
<td>Bacteremia</td>
<td>30 (7.2)</td>
<td>40 (9.5)</td>
<td>2.3</td>
<td>-1.4 to 6.1</td>
<td>0.22</td>
</tr>
<tr>
<td>Catheter-related sepsis</td>
<td>21 (5.0)</td>
<td>17 (4.0)</td>
<td>-1.0</td>
<td>-3.8 to 1.8</td>
<td>0.50</td>
</tr>
<tr>
<td>Septic shock</td>
<td>41 (9.8)</td>
<td>29 (6.9)</td>
<td>-2.9</td>
<td>-6.7 to 0.8</td>
<td>0.13</td>
</tr>
<tr>
<td>Hematologic‡</td>
<td>10 (2.4)</td>
<td>10 (2.4)</td>
<td>0</td>
<td>-2.1 to 2.1</td>
<td>1.00</td>
</tr>
<tr>
<td>Gastrointestinal§</td>
<td>13 (3.1)</td>
<td>19 (4.5)</td>
<td>1.4</td>
<td>-1.2 to 4.0</td>
<td>0.28</td>
</tr>
<tr>
<td>Neurologic¶</td>
<td>25 (6.0)</td>
<td>33 (7.9)</td>
<td>1.9</td>
<td>-1.6 to 5.3</td>
<td>0.28</td>
</tr>
<tr>
<td>Shock¶¶</td>
<td>67 (16.0)</td>
<td>55 (13.1)</td>
<td>-2.9</td>
<td>-7.7 to 1.8</td>
<td>0.23</td>
</tr>
<tr>
<td>Any complication</td>
<td>205 (49.0)</td>
<td>228 (54.3)</td>
<td>5.2</td>
<td>-1.5 to 12.0</td>
<td>0.12</td>
</tr>
</tbody>
</table>

- restrictive group: ECL if Hb < 7 g/dl, target Hb 7-9 g/dl
- liberal group: target Hb 10-12 g/dl

**NEJM 1999; 340: 409-17**

- **inclusion:**
  Hb < 9g/dl during first 72h of admission

- **duration of study 30 days:**
  - restrictive group: 2.6 ECL per patient
  - liberal group: 5.6 ECL per patient

**Reduction of 56 %**

- **primary endpoint:**
  30 days mortality (all causes)
RESULTS TRICC TRIAL

• significantly more pulmonary edema and AMI in the ‘liberal group’ (cfr table 3)
• mortality D30: restrictive group 18.7% - liberal group 23.3 % (p = 0.11)
• survival significantly better in 2 subgroups of the restrictive group:
  - APACHE II score ≤ 20
  - age < 55 yr

CONCLUSION:

TRICC trial: euvolemic intensive care adult patients benefit from a restrictive transfusion approach → **aim:** Hb concentrations between 7.0 and 9.0 g/dl
FOCUS trial: hip surgery and ECL transfusion

- **aim**: study the safety of restrictive transfusion strategy in older (hip-) surgery patients with history of or risk factors for cardiovascular disease.

- $n = 2016; \geq 50$ yr; Hb $< 10$ g/dl post-surgery
- restrictive (Hb: 8 g/dl) vs. liberal (Hb: 10 g/dl)

- **restrictive groep**: 3 x less ECL
- **no outcome difference** (primary outcome) = mortality or inability to walk around a room without human assistance on D60.
- **number of complications** equal in both groups

NEJM 2011; 365: 2453-62
Cochrane meta-analysis: n = 4000 surgery patients

- restrictive → significant decrease ‘hospital-mortality’; not mortality at D30 (p=0.1)
- restrictive → no prolongation of hospital stay.
- restrictive → ‘trend to’ less infections or pulmonary edema but not significant.

1) irradiated ECL

- gamma or X-rays (25 – 50 Gy)
- ↔ remaining lymphocytes after leukodepletion
- if immunocompromised patients ↔ TA-GvHD
Indications for irradiated blood components

- congenital immunodeficiency
- intra-uterine transfusion and exchange transfusion
- allogeneic (lifelong) and autologous (1 yr post) HSC transplantation
- solid organ Tx if immunosuppressive treatment with ATG
- M. Hodgkin, AA
- neoplasia if chemotherapy with purine-analogues (fludarabine, cladribine, pentostatine)
- (intrafamilial transfusions)
2) CMV-negative blood components

- **CMV-negative** = CMV seronegative donor
- **CMV-safe** = all leukodepleted blood components

2 indications for ‘double safety’:

- intra-uterine transfusions
- unrelated HSC-Tx with CMV-negative donor into CMV-negative recipient
3) washed erythrocytes

- repeatedly washed with cold, isotonic physiologic saline (NaCl 0,9%)

* discard all plasma, if:
  - plasma protein antibodies: eg. anti-IgA
  - severe allergic transfusion reactions
  - massive transfusion of neonati (K⁺ ↓)
Indications for the transfusion of platelets
General

- Platelet transfusions improve haemostasis in thrombocytopenic patients.

- 70% of the platelet transfusions in hospitals: prophylactic.

- If chronic BP transfusions: monitor efficacy!

- Pooled random donor BP or single donor BP: therapeutically equivalent.
Indications

- before surgery or invasive procedures in thrombocytopenic patients (transfusion threshold discussed later)

- stable chronic thrombocytopenia (MDS, AA, other): but → keep a low transfusion threshold to avoid HLA immunisation.

- massive transfusion: general agreement that the BP should not drop below 50000/μl.
Indications (2)

- ITP (immune mediated thrombocytopenia): only if life threatening bleeding. BP transfusions will then be combined with IVIg and steroids.

- DIC: in case of active bleeding or at high risk of bleeding: maintain BP > 50000/µl

- Neonatal immune thrombocytopenia: in addition to high dose IVIg, HPA-compatible platelets may be required (maintain BP count > 30000/µl)
NOT an indication

- ITP if no life threatening bleeding

- post transfusion purpura (PTP):
  high dose IVIg = treatment of choice

- heparin-induced thrombocytopenia (HIT): contra-indication (risk of inducing arterial or venous thrombosis)
NOT an indication (2)

- thrombotic thrombocytopenic purpura (TTP): contra-indication.
  - safer not to transfuse blood platelets
  - only risk-benefit if catheterisation needed (pre-apheresis)
  - consider BP transfusion if life threatening bleeding

- cardiopulmonary bypass (CPB): reduction in platelet counts because of hemodilution and transient platelet function impairment
  - prospective randomised studies: prophylactic BP transfusion is ineffective.
Thrombocytopenia

Transfusion trigger:

- keep $\text{BP} > 10000/\mu\text{l}$ if no risk factors for bleeding
- keep $\text{BP} > 20000/\mu\text{l}$ if risk factors for bleeding (fever, sepsis, ...)
- acute or recent important bleeding: keep $\text{BP} > 50000/\mu\text{l}$
- therapeutic dose op LMWH: keep $\text{BP} > 50000/\mu\text{l}$
- surgical intervention: $\text{BP} > 50000/\mu\text{l}$
- less invasive procedures (DVC, transjugular liverbiopsy): $\text{BP} > 30000/\mu\text{l}$
- major surgical procedures (CNS): keep $\text{BP} > 100000/\mu\text{l}$ (talk with the surgeon !)
Dose of platelets

• **standard dose**
  
  ➢ **pool** platelets: prepared from 4-6 buffy coats. Dose of end product is variable: between $2.5 \times 4 \times 10^{11}$ platelets.

  ➢ **single donor**: $4 \times 10^{11}$ platelets/unit

• **Slichter et al. NEJM 2010**  (PLADO trial).
  
  ➢ randomised trial, aim to study effect of the dose of transfused blood platelets on bleeding events in the setting of prophylactic BP transfusion

  ➢ $n = 1351$, 26 sites

  ➢ 3 groups: **low dose** ($1.1 \times 10^{11}/m^2$), **medium dose** ($2.2 \times 10^{11}/m^2$), **high dose** ($4.4 \times 10^{11}/m^2$)

  ➢ transfusion if thrombocytes $\leq 10000/\mu l$

  ➢ **primary end point**: bleeding grade 2 or more (WHO scale)
Dose of platelets (2)

- **Slichter et al. NEJM 2010**

result 1:
- incidence of higher grades of bleeding (grade 2 and more) were **similar among the 3 groups**.
- in the low dose group, more frequent transfusions were needed *(days to next transfusion: low dose = 1.1 d; medium dose = 1.9 d; high dose = 2.9 d).*

result 2:
- median number of platelets transfused was **significantly lower in group 1** *(total number of platelets transfused: low dose = 9.25 \times 10^{11}; medium dose = 11.25 \times 10^{11}; high dose = 19.63 \times 10^{11})*.

result 3:
- higher bleeding risk if BP < 5000/µl ➞ 25 % bleeding risk (gr 2 or more) vs. 17% if BP > 6000/µl.
Conclusion:

- prophylactic transfusions (trigger threshold of 10000/µl or lower):
  
  **platelet dose:** no significant effect on incidence of bleeding in patients with hypoproliferative thrombocytopenia.

- strategy of low-dose transfusion significantly reduces quantity of **platelets transfused**, which could preserve these scarce blood components, **but also increase the number of platelet transfusions**.
Prophylactic versus therapeutic

- **TOPPS** (Trial of Prophylactic Platelets)
  - non-inferiority study (randomized, open label) ; n = 600
  - non-prophylactic (NP, therapeutic) vs. prophylactic (P)

  ![Graph showing time to first grade 2-4 bleeding](image)

  - Hazard ratio, 1.30 (95% CI, 1.04–1.64) P=0.02
  - No prophylaxis (No prophy) vs. prophylaxis (Prophy)
  - Days since Randomization:
    - No. at Risk:
      - Prophylaxis: 298, 188, 170, 165
      - No prophylaxis: 300, 152, 140, 139

- Time to first grade 2-4 bleeding: significantly shorter in NP-arm

*NEJM 2013;368: 1771-80*
therapeutic BP-transfusion strategy could be considered in autologous HSC-Tx patients.

prophylactic BP-transfusions should be maintained in intensive chemo-AML patients and allogeneic HSC-Tx.
Indications for the transfusion of plasma
General

- plasma: for treating coagulation disorders, not to correct hypovolemia or for treating immunodeficiencies

- all plasma products must have undergone virus-inactivation (methylene blue) or pathogen reduction
Indications

➢ patients with massive bleeding (life-threatening) caused by trauma or surgery:
   (despite the lack of randomised controlled trials)
   • plasma should be given in adequate amounts to prevent further bleeding (10-15 ml/kg). Repeat if the bleeding persists.
   • at the same time: control source of bleeding, correct other factors leading to coagulopathy (acid-base disorders, hypothermia, hypocalcemia, anemia, thrombocytopenia).

➢ bleeding in patients with disturbed coagulation tests (or thrombolysis)

➢ bleeding in patients on coumarine anticoagulants:
   • Prothrombin complex concentrates (PCC) (PPSB or Octaplex®) are treatment of choice, together with vitamine K.
   • administration of plasma can be taken into consideration when PCC not available.
Indications (2)

- DIC: plasma can be taken into consideration for patients with DIC who are actively bleeding. **NOT** in order to correct abnormal coagulation tests.

- severe hypofibrinogenemia: infuse several plasma units!

- drug induced hypofibrinogenemia (e.g. asparaginase in ALL): 4 units are given if fibrinogen < 1 g/L.

- TTP: supply of the missing metalloproteinase enzyme!
Indications (3)

- isolated factor V or XI deficiency: also prophylactic
  *(cfr reimbursement criteria)*

- neonatal exchange transfusions in case of ABO incompatibility
NOT an indication

- prophylactic plasma transfusions to patients with normal coagulation tests submitted to high-risk surgery or invasive diagnostic procedures.

- volume expansion (in spite of being a good volume expander; we have colloids and crystalloids for that !)

- plasma exchange: use albumin or crystalloids !
Indications for granulocyte transfusions
Any indication?

- GT-induced acute lung injury: estimation of 10-15 % incidence
- fever in 17.5 % (Hübel et al. Transfusion 2002)
- allo-immunisation: HLA antibodies. Also monitor WBC antibodies. Stop GT when antibodies are present

- concerns now about the efficacy:
  - Cochrane review estimated a mild overall benefit (Stanword et al. Cochr Database Syst Rev. 2005)
  - Case reports: acceptable responses in infections refractory to conventional therapy
  - RING trial (ClinicalTrials.gov, NCT00627393) could answer the efficacy question

- benefit of GT in selected cases
1) GT may be indicated for patients with severe neutropenia who fulfil all of the following criteria:

- severe neutropenia, defined as ANC < 0.5 x 10^9/L due to congenital or acquired BM failure syndromes
- proven or highly probable fungal or bacterial infection that is unresponsive to appropriate antimicrobial therapy
- in whom neutrophil recovery is expected (ANC > 0.5 x 10^9/L) in the near future and/or in whom definitive therapy of curative potential is planned.
Restricted indications of GT (2)

2) therapeutic GT may also be indicated for patients with a known congenital disorder of neutrophil function, regardless of neutrophil count, with proven or highly probable fungal or bacterial infection, unresponsive to appropriate antimicrobial therapy.

3) GT should **NOT** be issued for therapeutic use in:

- patients with BM failure where neutrophil recovery is not anticipated to recur spontaneously and no further active treatment is planned.
- sepsis in the absence of neutropenia
- pyrexia of unknown origin
Thank you for your attention!
References: