Management of moderate Aplastic Anemia (MAA) and Supportive Care in Aplastic Anemia

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Potential conflicts of interest

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1. Funding  yes
2. Employment  no
3. Personal Financial Interest  no
**Definition of moderate Aplastic Anemia (MAA)**

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td><strong>BM cellularity</strong></td>
<td>&lt; 30%</td>
<td>&lt; 50%</td>
<td>hypocellular</td>
<td>20 - 50%;</td>
<td>hypocellular</td>
<td>25 – 50%</td>
</tr>
<tr>
<td><strong>PB cytopenias</strong></td>
<td>≥ 2 cell lines</td>
<td>≥ 2 cell lines</td>
<td>any</td>
<td>≥ 1 cell line,</td>
<td>≥ 2 cell lines</td>
<td>≥ 2 cell lines</td>
</tr>
<tr>
<td><strong>without meeting</strong></td>
<td></td>
<td>persisting ≥ 6</td>
<td></td>
<td>persisting &gt; 6</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>criteria for SAA</strong></td>
<td></td>
<td>weeks</td>
<td></td>
<td>months, negative</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Fanconi test</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>ANC</strong></td>
<td>&lt;1.2 G/l</td>
<td>&lt;1.5 G/l</td>
<td>&lt; 1.0 G/l</td>
<td>&lt; 1.0 G/L</td>
<td>&lt; 1.0 G/L</td>
<td>&lt; 1.0 G/L</td>
</tr>
<tr>
<td><strong>Platelet counts</strong></td>
<td>≤ 70 G/l</td>
<td>&lt; 100 G/l</td>
<td>&lt; 100 G/l</td>
<td>&lt; 50 G/L</td>
<td>&lt; 50 G/L</td>
<td></td>
</tr>
<tr>
<td><strong>Hb</strong></td>
<td>≤ 8.5 g/dL</td>
<td></td>
<td>&lt;9 g/dL</td>
<td></td>
<td>&lt;10 g/dl</td>
<td></td>
</tr>
<tr>
<td><strong>Reticulocytes</strong></td>
<td>&lt; 60 G/l</td>
<td>&lt; 40 G/l</td>
<td></td>
<td></td>
<td>&lt; 20 G/L</td>
<td></td>
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</tbody>
</table>
First step of MAA-managment: Proper diagnosis

Moderate Aplastic Anemia: To be, or not to be, that is the question.
Diagnostic algorithm MAA vs hypoplastic MDS

- Reactive-toxic (infection, vitamin deficiency, concomitant disease, drugs)
- Involvement of non-hematopoietic cells (neoplasm, infection, parasites)

Complete physical examination, detailed patient and family history
- Microscopic blood count, reticulocytes, bone marrow morphology

No specific findings: hMDS \(\Leftrightarrow\) AA?

- Inherited bone marrow failure syndromes (specific genomic testing)
- Aplastic Anemia, Pure Red Cell Aplasia, Amegakaryocytic Thrombocytopenia

Cytogenetics
- CD34+ BM-cells, SNP-array, somatic mutation testing

No specific findings

Course during follow up
Even the confirmed diagnosis of MAA has not to be the final one.
Immunosuppression in transfusion – dependent MAA : CSA mono vs ATG + CSA

But: Probability of survival with CSA alone 91% or CSA + ATG 93%.

Marsh J, Schrezenmeier H et al Blood 1999; 93 (7); ¹Death, nonresponse by 6 months, disease progression requiring a second course of immunosuppressive therapy or a stem-cell transplant, and relapse were considered treatment failures.
Alternative treatment options – a bouquet of possibilities

- Alemtuzumab\(^1\)
- Androgen\(^2\)
- Daciluzumab\(^3\)
- Levamisole\(^4\)
- TCM (e.g. Busuishengxue, Glycyrrhizin)\(^5,6\)
- TPO\(^7\)

Eltrombopagag in Moderate Aplastic Anemia (MAA) - Rationale

- Significant responses in 1 to all 3 cell lineages in ATGAM/CSA-refractory SAA (extended approval by FDA on 28th August 2014)

- Factors that predicted a response were:
  - less depressed baseline reticulocytes
  - immature platelet count

=> The chance for response might be even better in MAA which is characterized by a less depleted stem / progenitor cell compartment.

EMAA-trial: Efficiency and safety of thrombopoetin in moderate aplastic anemia

EMAA-trial: Design and treatment

**Type of trial:**
This is a prospective, randomized, placebo-controlled, double-blind multicenter study.

**Patient numbers:** 116 evaluable patients (58 each group)

**Treatment:**
Patients are randomized to receive either
Cyclosporine + Eltrombopag or Cyclosporine + placebo

Eltrombopag (or Placebo) starting dose: of 150 mg orally per day

Option of dose modification regarding to response
Prospective Eltrombopag-study in moderate AA - Proposed Trial Sites

France: Paris, Bordeaux
Germany: Ulm, Aachen, Berlin, Essen, Hamburg, Hannover
Italy: Genoa, Napels, Rome
Netherland: Leiden, Groningen
Switzerland: Basel
UK: London, Leeds

Planned study start: 01.12.2014
Treatment decision in MAA patients should be triggered by the clinical presentation in the individual patient in context of side effects of the various treatment regimes.
Suggestion of a treatment algorithm in MAA and MAA-PNH

MAA, MAA-PNH

Cytopenia

Symptomatic

Asymptomatic, transfusion-independent and ANC >1G/l, PLT >30G/l, Hb > 8.5 g/dl

Symptomatic

treatment according to severity and clinical condition (e.g. CSA, CSA+ATG, Alemtuzumab, androgens, Eltrombopag)

Asymptomatic

Hemolysis

Symptomatic

Complement inhibition (+ anti-coagulation in case of previous thromb-embolism)

Asymptomatic

Watch & wait

Supportive Care
Evidence –based?

- Randomized clinical trials on supportive care in AA are lacking.

- The most data are
  - related to immunocompromised hematological patients in general and not specifically to those with aplastic anemia
  - from retrospective studies / single-arm studies
  - or animal models!

- Conclusions regarding the supportive care of patients with aplastic anemia are mainly drawn by deduction.
Supportive Care – the underestimated treatment

<table>
<thead>
<tr>
<th>Group</th>
<th>Treatment period</th>
<th>Patient number</th>
<th>5 yr-survival responder</th>
<th>5-yr-survival non-responder (NR)</th>
<th>6 mo survival NR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td>12/1989 - 10/1996</td>
<td>43</td>
<td>91%</td>
<td>23%</td>
<td>61%</td>
</tr>
<tr>
<td>Group 2</td>
<td>11/1996 – 10/2002</td>
<td>51</td>
<td>92%</td>
<td>35%</td>
<td>82%</td>
</tr>
<tr>
<td>Group 3</td>
<td>11/2002 – 04/2008</td>
<td>80</td>
<td>94%</td>
<td>57%</td>
<td>89%</td>
</tr>
</tbody>
</table>
### Valdez et al 2011: Causes of death in the group of non-responders to IST

<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>Total deaths</td>
<td>84 (48)</td>
<td>37 (86)</td>
<td>25 (49)</td>
<td>22 (28)</td>
</tr>
<tr>
<td>Infection-related deaths</td>
<td>39 (22)</td>
<td>16 (37)</td>
<td>14 (27)</td>
<td>9 (11)</td>
</tr>
<tr>
<td>Fungal</td>
<td>17 (10)</td>
<td>8 (19)</td>
<td>7 (14)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Sepsis</td>
<td>16 (9)</td>
<td>4 (9)</td>
<td>6 (12)</td>
<td>6 (8)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>6 (3)</td>
<td>4 (9)</td>
<td>1 (2)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>6 (3)</td>
<td>1 (2)</td>
<td>2 (4)</td>
<td>3 (4)</td>
</tr>
<tr>
<td>MDS/leukemia</td>
<td>6 (3)</td>
<td>1 (2)</td>
<td>2 (4)</td>
<td>3 (4)</td>
</tr>
<tr>
<td>HSCT</td>
<td>16 (9)</td>
<td>5 (12)</td>
<td>4 (8)</td>
<td>7 (9)</td>
</tr>
</tbody>
</table>
Subgroup-analysis of the probability of death within 1 year in IST-non-responders

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Effect of covariate and risk of death&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline risk</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>Coefficient (β): 0.033  SD: 0.012  OR: 1.034  P: 0.004</td>
</tr>
<tr>
<td>ANC &lt;200 cells/µL</td>
<td>Coefficient (β): 2.056  SD: 0.633  OR: 7.818  P: 0.001</td>
</tr>
<tr>
<td>ARC</td>
<td>Coefficient (β): 0.114  SD: 0.234  OR: 1.120  P: 0.627</td>
</tr>
<tr>
<td>ALC</td>
<td>Coefficient (β): -0.297  SD: 0.399  OR: 0.743  P: 0.457</td>
</tr>
<tr>
<td>Platelet count</td>
<td>Coefficient (β): -0.096  SD: 0.267  OR: 0.908  P: 0.719</td>
</tr>
<tr>
<td>Bacteremia only</td>
<td>Coefficient (β): 0.919  SD: 0.542  OR: 2.508  P: 0.090</td>
</tr>
<tr>
<td>Fungal infection</td>
<td>Coefficient (β): 2.751  SD: 0.665  OR: 15.666  P: &lt;.001</td>
</tr>
</tbody>
</table>

<sup>a</sup> Valdez J. et al Clinical Infection Diseases 2011
Mould-active compared with fluconazole prophylaxis:

- significantly reduces invasive aspergillosis (RR 0.53, 95% CI 0.37–0.75; P=0.0004), occurrence and mortality of invasive fungal infections (RR 0.67, 95% CI 0.47–0.96; P=0.03)
- but increases AE (RR 1.95, 95% CI 1.24–3.07; P=0.004).
- and does not affect overall mortality (RR 1.0; 95% CI 0.88–1.13; P=0.96).

Antimycotic prophylaxis in neutropenic patients: Fluconazole or Mould active?
Antibiotic prophylaxis in Aplastic anemia

- Prophylactic antibiotics may prevent Gram-negative sepsis in SAA

- Antibiotic prophylaxis (especially fluoroquinolones) reduced mortality in afebrile neutropenic patients

- Prophylactic use of fluoroquinolones increased the risk for antibacterial resistance

- => antibiotic prophylaxis could be is recommended in patients with ANC < 0.2 G/l and should be considered for patients with ANC < 0.5 G/l.

Blood culture results

Prophylaxis for SAA is a controversial issue and practice varies widely. Common prophylactic recommendations might be:

- **In patients with ANC <0.2 G/l (to be considered at ANC <0.5 G/l):**
  - Antibiotic prophylaxis with fluoroquinolones
  - Antimycotic prophylaxis (Voriconazole or posaconazole appear to be more effective than fluconazole)
  - There are no general recommendations for antiviral or Pneumocystis jirovecii pneumonia prophylaxis

- **In patients after intensified immunosuppression until T-cell recovery:**
  - Antiviral prophylaxis with acyclovir or valacyclovir. CMV and EBV reactivation seems to be increased after alemtuzumab and rabbit ATG
  - Usage of PJP-prophylaxis depends on the individual centre. Nebulized pentamidine should be used (cotrimoxazole can be myelosuppressive).

- **In patients who undergo allogeneic HSCT:**
  - Standard procedures for prevention and treatment of infections after SCT should be followed
Vaccination strategies for Aplastic Anemia

- Strategies are not well defined except for patients undergoing transplantation.

- Support for concerns about immune activation by vaccination is very limited and is only based on case reports.

- Response to vaccination is likely to be poor and not recommended during profound leukopenia (neutrophils <0.5 × 10⁹/L, lymphocytes <0.7 × 10⁹/L) or intensified immunosuppressive therapy.

- Less severely affected patients should receive their age and situation appropriate vaccines. Pneumococci and influenza vaccines can be useful.

- **But:** Live vaccines (varicella, MMR, live influenza vaccine) should not be given while receiving immunosuppression.
Low bacteria diet

• The available data do not support the use of a special low bacteria diet in neutropenic patients

• We recommend to consider basic principles like:
  (1) washing hands before preparing food,
  (2) avoiding contamination of other food with raw meat, fish, chicken by storing or dishes and cutlery,
  (4) using of fresh food without a hint for molder,
  (5) consuming of pasteurized juices and dairy products;
  (6) avoiding uncooked meats, seafood, eggs and unwashed fruits and vegetables,
  (7) avoiding raw nuts and dried fruits (risk of fungal spores).

• These recommendations apply in particular to vSAA patients non-severe AA patients can have a standard diet.
Optimized hand and oral hygiene is highly efficient for the reduction of neutropenic infections!

- Protective isolation, including air quality control and barrier isolation with prophylactic antibiotics,
  ⇒ significant reduction in all-cause mortality

- Protective isolation, including air quality control and barrier isolation without prophylactic antibiotics:
  ⇒ no significant effect on mortality
  ⇒ No significant reduction of overall occurrence of infections

- exposure to construction areas should be avoided as outbreaks of aspergillus infections in patients exposed to sites of construction are well documented

Thus, barrier isolation and facilities with HEPA filtration as well as one or two beds rooms with en-suite facilities are not imperative but should be used if available.

Fever with neutropenia is an indication for immediate hospitalization!

Diagnostic procedures: physical examination, blood cultures and cultures from other relevant sites while chest X-ray is optional, but often useful.

Treatment must be started according to the local hospital guidelines without waiting for culture results.

In cases of persisting fever or suspected fungal infection, systemic antifungal therapy should be used early. In these cases CT scanning of the chest should be performed.

The use of short-term G-CSF may be beneficial during neutropenic fever.

In life threatening infections during neutropenia, the use of irradiated granulocyte transfusions should be discussed.
Transfusion therapy and prognosis of SCT

• Correlation of transfused units and Failure after Bone marrow transplantation

• But no discrimination between PRBC and PC (iron overload) and no leucocyte depletion

=> nevertheless: restrictive transfusion policy according to the principle “as much as necessary, as little as possible”

Champlin et al Blood Vol 73, 1989:606-613
The decision for transfusion should be based on clinical symptoms

**Platelet concentrates:**
- therapeutic transfusion in case of significant bleeding
- prophylactic transfusion when the platelet count is < 10 x 10^9/L (< 5 x 10^9/L)

Or

- < 20 x 10^9/L in the presence of fever, infection, outpatient

**Red blood cell concentrates:**
- hypoxic anemia
- based on symptoms and co-morbidities; quality of life
- transfusion trigger ranges mostly between 8,0-8,5 g/dl
- To avoid hypoxic cell damage hemoglobin levels < 6,0 g/dl are obligate transfusion triggers.
Universal leuko-reduction of blood products has reduced patient alloimmunization (erythrocyte-dependent immunization against minor histocompatibility antigens is not eliminated).

<table>
<thead>
<tr>
<th>Leukocyte-depleted blood products</th>
<th>non-leukocyte-depleted blood products</th>
</tr>
</thead>
<tbody>
<tr>
<td>n = 16 patients</td>
<td>n = 22 patients</td>
</tr>
<tr>
<td>2**/ 16 ELISA (12 %)</td>
<td>11 / 22 LCT (50 %)</td>
</tr>
<tr>
<td>1 / 16 LCT (6 %)</td>
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</tbody>
</table>

* 5 x 10⁶ WBC / unit
** no platelet refractoriness

p < 0.02

=> Use leukoreduced blood product to prevent HLA-Alloimmunization
- pre-storage leukoreduction (< 1 x 10⁶ residual leukocytes per unit)
- Non-sensitized patients can receive random donor platelet concentrates (PC)
- allo-sensitized patients with platelet refractarity should receive HLA- and/or HPA-matched PC

Irradiated blood products should be used to prevent HLA and non-HLA-alloimmunisation and ta-GvHD:

- during / after intensive immunosuppression (e.g. ATG, Alemtuzumab) until lymphocyte count recovers $> 1 \times 10^9/L$
- patients receiving allogeneic stem cell transplantation (at the latest at start of conditioning; in all patients who are transplant candidates ?)

Additionally, irradiation of blood products have to be done on:

- HLA-matched apheresis platelet concentrates
- all granulocyte concentrates

Gamma-irradiation can be replaced by pathogen-reduction
Chronic transfusions in Aplastic anemia

<table>
<thead>
<tr>
<th>Chron. transfusion dependency</th>
<th>Diagnosis</th>
<th>Med. age in years (min.-max.)</th>
<th>Sex (male/female)</th>
<th>SCT</th>
<th>Med. duration of transfusion therapy in mo. (min. – max.)</th>
<th>Med. number of transfused units (min. – max.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRBC</td>
<td>10 x AA, 2 x PNH, 1 x PRCA</td>
<td>68 (20-84)</td>
<td>7/6</td>
<td>0</td>
<td>17 (9 - 163)</td>
<td>40 (7 - 94)</td>
</tr>
<tr>
<td>PC</td>
<td>12 x AA</td>
<td>63 (20-76)</td>
<td>7/5</td>
<td>0</td>
<td>13 (6 - 171)</td>
<td>101 (16 – 328)</td>
</tr>
</tbody>
</table>

- There was no hint for a decrease of clinical efficacy during follow up
- Median increment after the first PC: 51 (17-68) G/l.
- Median increase after 2 unit PRBC: 2.0 (0,6-3,7) g/dl
- No new HLA-antibodies were observed.
- 2/12: new red cell alloantibodies (anti-Fy(a); anti-Lu(a); anti-Kp(a))
- No seroconversion for HBV/ HCV/ HIV, 1/10 CMV-seroconversion
- Ferritin-increase during follow up: 235 (10-1713) to 1469 (20-3146) ng/mL
Iron Overload and Iron Chelation in Patients with Aplastic Anemia

- Iron overload has negative impact on morbidity and mortality (Takatoku et al., 2007; Lee et al., 2008; Kim et al., 2009)
- EPIC Trial (Evaluation of Patients’ Iron Chelation with Exjade)
  - n = 1.744 patients
  - subgroup of 116 patients with AA
  - Inclusion criteria: Ferritin > 1.000 ng/ml or > 100 ml/kg RBC
  - and liver-iron concentration > 2 mg Fe/g dry weight

- => significant decrease of serum ferritin after 1 year deferasirox therapy

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients with AA (n = 116)</th>
</tr>
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<tbody>
<tr>
<td>Mean age ± SD, y</td>
<td>33.3 ± 17.1</td>
</tr>
<tr>
<td><strong>Age group, y</strong></td>
<td></td>
</tr>
<tr>
<td>2 to less than 16, n (%)</td>
<td>16 (13.8)</td>
</tr>
<tr>
<td>16 or older, n (%)</td>
<td>100 (86.2)</td>
</tr>
<tr>
<td>Male/female, n</td>
<td>67:49</td>
</tr>
<tr>
<td>Race (White/Black/Asian), n</td>
<td>32:4:80</td>
</tr>
<tr>
<td>Chelation-naive, n</td>
<td>79 (68.1)</td>
</tr>
<tr>
<td><strong>Previous iron chelation therapy, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>DFO monotherapy</td>
<td>31 (26.7)</td>
</tr>
<tr>
<td>DFO + deferiprone combination</td>
<td>6 (5.2)</td>
</tr>
<tr>
<td>Mean duration of previous iron chelation therapy ± SD, y</td>
<td>4.3 ± 5.8</td>
</tr>
<tr>
<td>Mean duration of transfusion history ± SD, y</td>
<td>6.1 ± 5.7</td>
</tr>
<tr>
<td>Mean no. of transfusion sessions in the year before study entry ± SD</td>
<td>12.5 ± 13.0 (n = 114)</td>
</tr>
<tr>
<td>Mean total volume red blood cells transfused in the year before study entry ± SD, mL/kg</td>
<td>116 ± 179 (n = 112)</td>
</tr>
<tr>
<td>Median baseline serum ferritin (range), ng/mL</td>
<td>3254 (908-25 346) (n = 115)</td>
</tr>
</tbody>
</table>
EPIC Trial: Iron Chelation Therapy is Associated with Improvement of Hematopoisis AA-patients

Mean absolute neutrophil and platelet counts during deferasirox treatment.

Hematologic responses after 1 year with deferasirox treatment (72 patients).
Iron Chelation Therapy Associated with Improvement of Hematopoisis in Transfusion-Dependent Patients

Koh et al., J Pediatr Hematol Oncool 32:611; 2010
Oliva et al., Transfusion 50: 1568-1570; 2010
Iron chelation in Aplastic Anemia

- Iron chelation is effective in AA
- Reduction of iron overload depends on iron intake and dose of chelator
- Desferrioxamine or deferasirox may be used
- Deferiprone is not routinely recommended in AA (incidence of agranulocytosis)
- Careful monitoring of renal function, especially in pts receiving concomitant ciclosporine
- Venesection should be performed in patients with iron overload who achieve transfusion independence after treatment
- AA patients may benefit from iron chelation in terms of hematologic response.

Psychological support

• Mental constitutional is an important point for quality of life

• AA-patients have a special burden by the rarity of the disease
  => careful explanation about the nature of the disease, treatment, prognostic and social impact for the patients and their families.

• Relevant portion of patients with persisting cytopenia
  => explanation of quality of life as therapy aim

• “rules for a working social life”
  => avoidance of unnecessary cuts of social contacts
  => life as normal as possible as important support for psychological health.
  => Adapted physical activity and sports are often helpful in this context.

• As the diagnosis of aplastic anemia is a life changing experience some patients will need professional psychological support.

• For some patients it is helpful to be in contact with other aplastic anemia patients.
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Institute of Clinical Transfusion Medicine and Immunogenetics Ulm
& German Red Cross Blood Donor Services Baden-Wuerttemberg - Hessia

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Thanks for your attention!
Antimycotic prophylaxis in neutropenic patients receiving cytotoxic therapy

Time to definitive or probable invasive fungal infection

=> prophylactic antifungals should be used in general for patients with very severe aplastic anemia
Antimycotic prophylaxis in neutropenia

Metaanalysis: Antifungal prophylaxis in neutropenic patients after chemotherapy
- Fungal related mortality (64 randomized trials)

- Fluconazole vs Placebo => RR 0.49 (95% CI:0.32-0.75) p= 0.0009
- Itraconazole suspension vs Placebo => RR 0.44 (95% CI:0.20-0.99) p = 0.05
- i.v. Ambisome vs Placebo => RR 0.29 (95% CI:0.10 – 0.87) p= 0.03
- Total => RR 0.55 (95% CI:0.41-0.74) p < 0.0001

=> prophylactic antifungals should be used in neutropenic patients
Granulocyte transfusions in severe aplastic anemia

Table 3. Survival of SAA patients received granulocytes and G-CSF therapy.

<table>
<thead>
<tr>
<th></th>
<th>N. of patients</th>
<th>Survival at 30d</th>
<th>Survival at 90d</th>
<th>Survival at 180d</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>56</td>
<td>50(89%)</td>
<td>39(70%)</td>
<td>37(66%)</td>
</tr>
<tr>
<td>Fungal</td>
<td>31</td>
<td>27(87%)</td>
<td>18(58%)</td>
<td>16(52%)</td>
</tr>
<tr>
<td>Bacterial</td>
<td>25</td>
<td>23(92%)</td>
<td>21(84%)</td>
<td>21(84%)</td>
</tr>
</tbody>
</table>

- Granulocyte replacement during severe neutropenic infections may have an adjunctive role in severe infections in SAA patients as a possible way to bridge the gap between specific treatment and neutrophil recovery.
- HLA alloimmunization is not an absolute contraindication.
- Prophylactic granulocyte transfusion may reduce the risk of mortality from infection.
- Overall mortality was not affected.
Irradiated blood products in Aplastic Anemia

Effects of blood transfusions from the marrow donor on the outcome of subsequent marrow grafts in DLA-identical canine littermates

<table>
<thead>
<tr>
<th>Pretransplant transfusions of 50 ml heparinized whole blood</th>
<th>Number of dogs</th>
<th>Marrow engraftment(^a)</th>
<th>Percent rejecting</th>
</tr>
</thead>
<tbody>
<tr>
<td>None(^b)</td>
<td>62</td>
<td>61</td>
<td>1</td>
</tr>
<tr>
<td>Untreated donor blood at days -24, -17, and -10(^b)</td>
<td>27</td>
<td>0</td>
<td>27</td>
</tr>
<tr>
<td>20 Gy-treated blood at days -24, -17, and -10(^b)</td>
<td>10</td>
<td>9</td>
<td>1</td>
</tr>
<tr>
<td>20 Gy-treated blood at days -48, -41, and -34 and untreated blood at days -24, -17, -10</td>
<td>4</td>
<td>0</td>
<td>4</td>
</tr>
</tbody>
</table>

\(^a\) Recipients conditioned with 920 cGy TBI on the day of transplant (day 0).
\(^b\) Previously reported results.
\(^c\) \(P\) value calculated by Monte Carlo simulation.

HGF administration did not decrease the occurrence of

- clinically documented infections (RR 1.10; 95% CI 0.90-1.33)
- severe infections (RR 0.88; 95% CI 0.58 – 1.34)
Granulocyte Growth factors in Aplastic Anemia and response

HGF administration did not increase rate of hematologic response

=> no indication for treatment of AA with hematopoietic growth factors alone