Supportive Care for Aplastic Anemia

• Transfusions
  - RBC
  - Platelet concentrates
  - Granulocyte concentrates

• Iron chelation

• Prophylaxis and treatment of infection

• Hematopoietic growth factors
Supportive Care for Aplastic Anemia

Evidence based?

- data related to immunocompromised hematological patients in general and not specifically to those with aplastic anemia!

- data from retrospective studies / single-arm studies

- animal models

→ conclusions regarding the supportive care of patients with aplastic anemia are mainly drawn by deduction.

randomized clinical trials on supportive care in AA are lacking.

Supportive Care in Severe and Very Severe Aplastic Anemia

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Bone Marrow Transplantation, in press.
Advances in Supportive Treatment of Aplastic Anemia

• Transfusions
  - RBC
  - Platelet concentrates
  - Granulocyte concentrates

Gamma-Irradiation: yes / no ?

• Iron chelation

• Prophylaxis and treatment of infection

Transfusion Policy in Aplastic Anemia

• Indication

• Irradiated blood products

• Adverse events
  • Alloimmunization (HLA, mHA)
  • Iron overload
Actuarial probability of graft failure in AA patients according to number of pretransplant transfusions

**MONTHS**

![Graph showing actuarial probability of graft failure](image)

*Fig 2. Actuarial probability of graft failure in patients receiving cyclophosphamide alone for pretransplant conditioning according to (A) whether corticosteroids were used to treat aplastic anemia prior to transplantation and (B) number of pre-transplant transfusions.*

**Period: 1978-1986**

*Champlin et al., Blood 73: 606-613 (1989)*

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Impact of number of pre-transplant transfusions on outcome after BMT

![Graph showing impact of transfusions on survival](image)

**Similar results:** A. Piccin, ... S. McCann, Ir. J. Med. 174: 13, 2005

J.C. Hernandez-Boluda et al., Haematologica 84:26, 1999
Transfusion Policy in Aplastic Anemia

- **Recommendation I** -

- **Restrictive Transfusion policy**

  **Platelet concentrates:**

  - therapeutic transfusion in case of significant bleeding
  - prophylactic transfusion when the platelet count is $< 10 \times 10^9/L$ ($< 5 \times 10^9/L$) or $< 20 \times 10^9/L$ in the presence of fever, infection,

  **Red blood cell concentrates:**

  - hypoxic anemia
  - based on symptoms and co-morbidities; quality of life

**Transfusion of Pre-Storage Leukodepleted* Blood Products Reduces HLA Alloimmunization in Aplastic Anaemia**

<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>
<td></td>
</tr>
</tbody>
</table>

* * < 5 x $10^6$ WBC / unit

** no platelet refractoriness

$p < 0.02$

**Chronic Transfusion Support in AA patients**

<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, 2x PNH, 1x 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>

- Median increment after the first PC was 51 (17-68) G/l.
- There was no hint for a decrease of clinical efficacy during PC transfusion therapy.
- No new HLA-antibodies were observed.

- 2/12: new red cell alloantibodies (anti-Fy(a); anti-Lu(a); anti-Kp(a))
- Hemoglobin increase after transfusion of 2 units:
  - first transfusion: 2.0 (0.6-3.7) g/dl, last follow up: 2.0 (0.9-3.5) g/dl

- No seroconversion for HBV/ HCV/ HIV, 1/10 seroconversion for CMV
- Ferritin prior to first transfusion: 235 (10-1713), last transfusion: 1469 (20-3146)

_B.Höchsmann et al._

**Transfusion Policy in Aplastic Anemia**

- **Recommendation II** -

- **Use leukoreduced blood products to prevent HLA alloimmunisation**
  - pre-storage leukoreduction (< 1 x 10⁶ residual leukocytes per unit)
  - non-sensitized patients can receive random donor platelets
  - allo-sensitized patients with platelet refractoriness should receive HLA- and/or HPA-matched platelet concentrates.
Rationale for giving only irradiated blood products:

- prevention of transfusion-associated GvHD (in particular in the context of ATG treatment)
- reduction of sensitization to HLA and non-HLA antigens from multiple transfusions

### Irradiated Blood Products in Aplastic Anaemia

#### 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&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Percent rejecting</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>None&lt;sup&gt;b&lt;/sup&gt;</td>
<td>62</td>
<td>61</td>
<td>1</td>
</tr>
<tr>
<td>Untreated donor blood at days -24, -17, and -10&lt;sup&gt;b&lt;/sup&gt;</td>
<td>27</td>
<td>0</td>
<td>27</td>
</tr>
<tr>
<td>20 Gy-treated blood at days -24, -17, and -10&lt;sup&gt;b&lt;/sup&gt;</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>

<sup>a</sup> Recipients conditioned with 920 cGy TBI on the day of transplant (day 0).

<sup>b</sup> Previously reported results.

<sup>c</sup> P value calculated by Monte Carlo simulation.

Bean et al., Transplantation 61: 334-335 (1996)
Irradiated Blood Products in Aplastic Anaemia

Survey EBMT AA WP (J. Marsh)

n = 14 centres (12 Europe, 2 US)

6 / 12 (50 %) leukocyte depleted blood products irrespective of treatment
12 / 14 (85 %) irradiated blood products after ATG treatment

Recommendation for use of irradiated blood products after ATG in national guidelines, e.g.
- BCSH Guidelines for Diagnosis and Management of AA
  (www.bcsghguidelines.com)
- German Hemotherapy Guidelines

**But**: no recommendation how long this practice should continue after ATG

**Proposal**: until lymphocyte count recovers > 1.0 x 10^9/L

Marsh et al., Bone Marrow Transplantation 43 (S1): S57 (2009)

Transfusion Policy in Aplastic Anemia
- **Recommendation III** -

- Irradiated blood products to prevent HLA alloimmunisation and ta-GvHD
  - during / after ATG treatment (until lymphocyte count recovers >1 x 10^9/L)
  - during and after other intensive immunosuppressive treatment, e.g. alemtuzumab
  - patients receiving allogeneic stem cell transplantation (at the latest at start of conditioning; in all patients who are transplant candidates ?)
  - HLA-matched apheresis platelet concentrates
  - all granulocyte concentrates

- **Gamma-irradiation can be replaced by pathogen-reduction (platelets; FFP)**
Does efficient universal leukoreduction completely abrogate alloimmunization and prevent graft rejection?

Transplant Rejection in a Mouse Model - RBC

Leukoreduction of transfused blood does not prevent rejection

**Conclusion:**
1. Transfusion of RBC units prior to transplant induce BMT rejection.
2. Leukodepletion does not prevent BMT rejection.

*Desmarests et al., Blood 114: 2315-2322 (2009)*
Transplant Rejection in a Mouse Model - PC
Leukoreduction of transfused blood does not prevent rejection

Conclusion: 1. Transfusion of mHA mismatched PLT prior to transplant induce BMT rejection. 2. Both direct (via recipient APC) as indirect (via donor APC) seems possible. 2. Leukodepletion does not prevent BMT rejection.


Transplant Rejection in Animal Models
Indirect presentation pathway is sufficient to induce BM rejection

Patenski et al., Tissue Antigens 79: 237-245 (2012)
Granulocyte Transfusion in Severe Aplastic Anemia

n = 32 pts; 379 granulocyte concentrates/median 9 granulocyte concentrates/pt.
Mean granulocyte dose: $6.8 \pm 2.3 \times 10^{10}$ cells
Infections: n = 18 bacterial; n = 19 fungal

<table>
<thead>
<tr>
<th>Response</th>
<th>Day 7 Survival to Discharge</th>
<th>Day 30 Survival to Discharge</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>10 (30%)</td>
<td>11 (33%)</td>
</tr>
<tr>
<td>PR</td>
<td>10 (30%)</td>
<td>9 (27%)</td>
</tr>
<tr>
<td>Stable or progression</td>
<td>13 (40%)</td>
<td>13 (41%)</td>
</tr>
</tbody>
</table>

Strong association with hematopoietic recovery:
14 recovery of hemopoiesis: 13 survivors (93%)
18 without recovery of hemopoiesis: 4 survivors (22%)

Quillen et al., haematologica 94: 1661-1668 (2009)

Granulocyte Transfusion in Severe Aplastic Anemia

- Granulocyte replacement 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 to granulocyte transfusions.
Supportive Treatment of Aplastic Anemia

Granulocyte transfusions for preventing infections in patients with neutropenia or neutrophil dysfunction

Authors’ conclusions:

• Prophylactic granulocyte transfusions (> $1 \times 10^{10}$) may reduce the risk of mortality from infection.

• Overall mortality was not affected.

Massey et al., Cochrane Database Syst. Rev. 2009 Jan 21;(1): CD005341

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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; 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

![Table 1. Demographic and baseline patient characteristics](Lee et al., Blood 116: 2448-2454 (2010))

![Median serum ferritin at baseline and at 1 year of deferasirox treatment](Lee et al., Blood 116: 2448-2454 (2010))

![Mean absolute neutrophil and platelet counts during deferasirox treatment](Lee et al., Blood 116: 2448-2454 (2010))
Iron Chelation Therapy Associated with Improvement of Hematopoisis in Transfusion-Dependent Patients (case reports)

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

Iron Overload and Iron Chelation in Patients with Aplastic Anemia

- Recommendation -

- Iron chelation is generally effective in reducing iron burden in AA.
- Reduction in serum ferritin is a function of transfusional iron intake and dose of chelator.
- Desferrioxamine or deferasirox may be used.
  Deferiprone is not routinely recommended in AA (relatively high incidence of agranulocytosis)
- Careful monitoring of renal function is necessary in patients who are receiving concomitant ciclosporine and deferasirox.
- 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 erythroid response.
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- Prophylaxis and treatment of infection

- Hematopoietic growth factors

Improved survival in SAA in the past two decades

Valdez et al., Clinical Infectious Diseases: 726-735 (2011)
### Infections

#### Frequency of infections in patients with SAA

- **Invasive fungal infections**
- **Bacterial infections**
- **Viral infections**

#### Organisms identified in blood cultures obtained from patients with SAA

- **Coagulase negative Staph.**
- **Staph. aureus**
- **E. faecalis / E. faecium**
- **Other gram positive bacteria**
- **Gram negative bacteria**

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**Valdez et al., Clinical Infectious Diseases: 726-735 (2011)**

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### Changing pattern of infections in SAA in the past two decades

### Antibiotic prophylaxis for bacterial infections in afebrile neutropenic patients following chemotherapy

- **Significant reduction in the risk of all-cause mortality:**
  - RR 0.66, 95% CI 0.55 – 0.79; n=5635 patients; 46 trials; NNT 34
  - Greatest effect was seen in the quinolone prophylaxis subgroup
  - RR 0.54, 95% CI 0.40 – 0.74; n=3776; 19 trials
  - Tests for subgroup differences were not significant (by disease status; by timing of prophylaxis initiation; by type of prophylaxis (except for norfloxacin))

- **Significant reduction in the risk of infection-related death**
  - RR 0.61, 95% CI 0.48 – 0.77; n=5777 patients; 43 trials; NNT 48

- **Significant reduction in occurrence of febrile episodes**
  - RR 0.80, 95% CI 0.74 – 0.87; n=6658 patients; 54 trials; NNT 7
  - Only chinolones and TMP-SMZ with significant reduction

- **Significant reduction in clinically and microbiologically documented infection**
  - Clinical: RR 0.65, 95% CI 0.56 – 0.76;
  - Microbiological: RR 0.51; 95 CI 0.42-0.62; NNT 7
  - Chinolones, TMP-SMZ and other systemic antibiotics with significant reduction, but not nonadsorbables.

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**Gafter-Gvili et al., Cochrance Data base of Systematic Reviews, 2012, issue 1**
Infection-related mortality: Fluoroquinolones versus placebo or no intervention

<table>
<thead>
<tr>
<th>Study, Year (Reference)</th>
<th>Quinolones, n/n</th>
<th>Placebo, n/n</th>
<th>RR (Fixed) (95% CI)</th>
<th>Weight, %</th>
<th>RR (Fixed) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleijfer et al., 1980 (23)</td>
<td>0/53</td>
<td>9/52</td>
<td>25.80</td>
<td>0.05 (0.00-0.87)</td>
<td></td>
</tr>
<tr>
<td>Karp et al., 1987 (16)</td>
<td>6/35</td>
<td>3/33</td>
<td>8.31</td>
<td>1.89 (0.51-6.93)</td>
<td></td>
</tr>
<tr>
<td>Schroeder et al., 1992 (22)</td>
<td>0/40</td>
<td>2/35</td>
<td>7.16</td>
<td>0.08 (0.01-3.54)</td>
<td></td>
</tr>
<tr>
<td>Talbot et al., 1993 (24)</td>
<td>1/62</td>
<td>2/57</td>
<td>5.61</td>
<td>0.46 (0.04-4.93)</td>
<td></td>
</tr>
<tr>
<td>Moreau et al., 1995 (94)</td>
<td>0/44</td>
<td>0/44</td>
<td>Not estimable</td>
<td>Not estimable</td>
<td></td>
</tr>
<tr>
<td>Carlsen et al., 1997 (13)</td>
<td>0/45</td>
<td>0/45</td>
<td>Not estimable</td>
<td>Not estimable</td>
<td></td>
</tr>
<tr>
<td>Thomas et al., 2000 (25)</td>
<td>5/99</td>
<td>5/52</td>
<td>17.64</td>
<td>0.53 (0.16-1.73)</td>
<td></td>
</tr>
<tr>
<td>Novoa et al., 2001 (20)</td>
<td>0/36</td>
<td>5/34</td>
<td>15.21</td>
<td>0.09 (0.00-1.50)</td>
<td></td>
</tr>
<tr>
<td>Tjan-Heijnen et al., 2001 (26)</td>
<td>0/82</td>
<td>5/79</td>
<td>15.07</td>
<td>0.09 (0.00-1.56)</td>
<td></td>
</tr>
<tr>
<td>Lee et al., 2002 (17)</td>
<td>2/46</td>
<td>2/49</td>
<td>5.21</td>
<td>0.17 (0.16-7.25)</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>542</td>
<td>480</td>
<td>100.00</td>
<td>0.38 (0.21-0.69)</td>
<td></td>
</tr>
<tr>
<td>Total events: 14 (quinolones), 33 (placebo)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for heterogeneity: chi-square = 11.41 (P = 0.12), I^2 = 38.6%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 3.20 (P = 0.001)</td>
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</tbody>
</table>


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=.0009
- Itraconazole suspension vs. Placebo: RR 0.44 (95% CI: 0.20-0.99) p=.05
- i.v. Ambisome vs. Placebo: RR 0.29 (95% CI: 0.10-0.87) p=.03

(Not significant Itraconazole capsules, i.v. Ambisome and Ketokonazole vs. Placebo).

TOTAL: RR 0.55 (95% CI: 0.41-0.74) p=<.0001

Subgroup analysis: acute leukemia patients and patients after stem cell transplantation:
- Reduction in fungal-related mortality and documented invasive fungal infections
- Allogeneic stem cell transplantation: reduction in all-cause mortality.

Posaconazole reduced all cause mortality, fungal-related mortality and invasive fungal infections when compared with fluconazole. Robenshtok et al., J Clin Oncol. 25:5471 5489 ; 2007

Antifungal prophylaxis:
- Significant reductions in proven fungal infections
- Significant reductions in fungal-related mortality
- Overall mortality was not affected

Ziakis P.D. et al., Clinical Therapeutics 32:2316; 2010
Metaanalysis:
Antifungal prophylaxis in neutropenic patients with Hematological malignancies
Comparing itraconazol and fluconazole
(9 randomized clinical trials)

Fluconazole vs. Itraconazole

<table>
<thead>
<tr>
<th></th>
<th>RR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fungal infections</td>
<td>1.34</td>
<td>1.08-1.67</td>
<td>.0009</td>
</tr>
<tr>
<td>invasive fungal infections</td>
<td>1.33</td>
<td>1.02-1.73</td>
<td>.03</td>
</tr>
<tr>
<td>fungal-related mortality</td>
<td>1.28</td>
<td>0.80-2.07</td>
<td>.31</td>
</tr>
<tr>
<td>overall mortality</td>
<td>0.95</td>
<td>0.77-1.17</td>
<td>.64</td>
</tr>
</tbody>
</table>

Significantly less patients were withdrawn from the studies due to development of adverse events with fluconazol compared to itraconazol.

J. Wang et al., Med Oncol. 27:1082-1088; 2010

Metaanalysis:
Infection control interventions for cancer patients after chemotherapy

- Protective isolation, including air quality control, prophylactic antibiotics, and barrier isolation brought about a significant reduction in all-cause mortality (RR 0.60 (95% CI 0.50-0.70))

- Inclusion of prophylactic antibiotics was necessary to show the effect on mortality.

- Control of air quality and barrier isolation (without prophylactic antibiotics):
  - no significant effect on mortality
  - significant reduction of clinically or microbiologically document infection
  - control of air quality or barrier isolation alone did not reduce overall occurrence of infection

Hematopoietic Growth factors in AA

- no indication for treatment of AA with hematopoietic growth factors alone

- HGF as adjunct to immunosuppressive treatment
  - improvement of hematopoietic response
  - reduction of infections
  - reduction of relapse of AA


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)
Prevention of infections in AA

- **Recommendation (for patients with < 0.5 x 10⁹/L)** -

  - nursing in isolation when in hospital
  - Prophylactic antibiotics should be used (quinolones or two non-absorbable antibiotics).
  - Antifungal prophylaxis should be used (either with fluconazole, itraconazole or posaconazole).
  - No indication for routine prophylaxis against *Pneumocystis jirovecii*
  - No indication for prophylactic G-CSF

Supportive Care for AA

Thank you for your attention!