Recent Advances in Supportive Treatment of Aplastic Anemia

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EBMT Educational Day
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German Red Cross Blood Transfusion Service Baden-Württemberg – Hessen

Institute of Transfusion Medicine, University of Ulm
Advances in Supportive Treatment of Aplastic Anemia

- Transfusions
  - RBC
  - Platelet concentrates
  - Granulocyte concentrates

- Iron chelation

- Prophylaxis and treatment of infection

- Hematopoietic growth factors
Advances in Supportive Treatment of Aplastic Anemia

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  - Granulocyte concentrates
- Iron chelation
- Prophylaxis and treatment of infection
- Hematopoietic growth factors
Transfusion Policy in Aplastic Anemia

Severity of disease (bone marrow failure) \(\rightarrow\) number of transfusions

\[\downarrow\]

RBC + PC + GC \(\rightarrow\) RBC

\[\downarrow\]

immunological consequences \(\rightarrow\) iron overload

\[\downarrow\]

\[\downarrow\]

Final Outcome
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 pretransplant transfusions.

Champlin et al., Blood 73: 606-613 (1989)
Impact of number of pre-transplant transfusions on outcome after BMT
Impact of number of pre-transplant transfusions on outcome after BMT

Table 3. Variables of prognostic significance for survival in univariate analysis.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Alive/total (%)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient's age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 30 years</td>
<td>2/9 (22%)</td>
<td>0.007</td>
</tr>
<tr>
<td>&lt; 30 years</td>
<td>26/40 (65%)</td>
<td></td>
</tr>
<tr>
<td>Sex mismatch</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female to male</td>
<td>8/18 (44%)</td>
<td>0.09</td>
</tr>
<tr>
<td>Others</td>
<td>20/31 (65%)</td>
<td></td>
</tr>
<tr>
<td>Interval diagnosis-BMT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 2 months</td>
<td>11/27 (41%)</td>
<td>0.01</td>
</tr>
<tr>
<td>&lt; 2 months</td>
<td>17/22 (77%)</td>
<td></td>
</tr>
<tr>
<td>No. previous transfusions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 10 units</td>
<td>19/39 (46%)</td>
<td>0.01</td>
</tr>
<tr>
<td>&lt; 10 units</td>
<td>9/10 (69%)</td>
<td></td>
</tr>
<tr>
<td>Refractoriness to platelets</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1/7 (14%)</td>
<td>0.02</td>
</tr>
<tr>
<td>No</td>
<td>27/42 (64%)</td>
<td></td>
</tr>
<tr>
<td>GvHD prophylaxis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MTX</td>
<td>11/25 (44%)</td>
<td>0.08</td>
</tr>
<tr>
<td>CSA</td>
<td>17/24 (71%)</td>
<td></td>
</tr>
<tr>
<td>Plasmaphoresis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>2/8 (25%)</td>
<td>0.02</td>
</tr>
<tr>
<td>No</td>
<td>26/41 (63%)</td>
<td></td>
</tr>
</tbody>
</table>

*Probability of survival.


J.C. Hernandez-Boluda et al., Haematologica 99: 84
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, infections or $< 50 \times 10^9/L$ during ATG treatment

**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 10⁶ 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)

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**B. Höchsmann et al.,**
Transfusion Policy in Aplastic Anemia

- Recommendation II -

• Use leukoreduced blood products to prevent HLA alloimmunisation
  
  - pre-storage leukoreduction (< $1 \times 10^6$ 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.
Irradiated Blood Products in Aplastic Anemia

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 = 13 centres (11 Europe, 2 US)

6 / 13 (46 %) LDBP irrespective of treatment
11 / 13 (85 %) irradiated blood products

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

But: no recommendation how long this practice should continue after ATG
Proposal: until lymphocyte count recovers > 1.0 x 10⁹/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
  - during / after ATG treatment (until lymphocyte count recovers >1 x 10^9/L)
  - in all patients who are transplant candidates?
  - all granulocyte concentrates must be irradiated
Transplant Rejection in a Mouse Model

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.

*Desmaret et al., Blood 114: 2315-2322 (2009)*
A. Direct antigen presentation by donor white blood cells

B. Indirect presentation of donor RBC antigens by recipient antigen-presenting cells

Chen, A. R. Blood 2009;114:2209-2210
Transplant Rejection in a Mouse Model

Indirect presentation pathway is sufficient to induce BM rejection

BM donor
- Strain: BALB.B
- MHC: H-2\(^b\)
- (5 x 10\(^6\) whole BM cells)

Recipient
- Strain: B6 recipient
- MHC: H-2\(^b\)
- 650 Gy

RBC donor
- Strain: BALB/c
- MHC: H-2\(^d\)

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Desmaret et al., Blood 114: 2315-2322 (2009)
Transplant Rejection in a Mouse Model

Observation:

1. Transfusions of RBC units prior to stem cell transplantation cause BMT rejection.

2. Leukodepletion does not prevent BMT rejection.

Explanation:

- mHA on RBC cause rejection.

- mHA on residual WBC cause rejection
  (residual WBC in this model correspond to $2.5 \times 10^6$ WBC / unit at a human scale).
Transplant Rejection in a Mouse Model

Leukoreduction prevents BMT rejection induced by a leukocyte-specific mHA

BM donor | Recipient | RBC donor
---|---|---
Strain: Male B6 (5 x 10^6 whole BM cells) | Female B6 650 Gy | Male B10.BR
MHC: H-2^b | H-2^b | H-2^k
mHA: HY | --- | HY

Desmaret et al., Blood 114: 2315-2322 (2009)
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</th>
<th>Survival to Discharge</th>
<th>Day 30</th>
<th>Survival to Discharge</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>10 (30%)</td>
<td>9/10 (90%)</td>
<td>11 (33%)</td>
<td>11/11 (100%)</td>
</tr>
<tr>
<td>PR</td>
<td>10 (30%)</td>
<td>6/10 (60%)</td>
<td>9 (27%)</td>
<td>7/9 (78%)</td>
</tr>
<tr>
<td>Stable or progression</td>
<td>13 (40%)</td>
<td>4/13 (31%)</td>
<td>13 (41%)</td>
<td>1/13 (8%)</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.
Advances in Supportive Treatment of Aplastic Anemia

• Transfusions
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  - Granulocyte concentrates

• Iron chelation

• Prophylaxis and treatment of infection

• Hematopoietic growth factors
Transfusion Policy in Aplastic Anemia

Severity of disease (bone marrow failure) → number of transfusions

→ RBC + PC + GC
→ RBC

Immunological consequences → iron overload

Final Outcome
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>
<thead>
<tr>
<th>Table 1. Demographic and baseline patient characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristic</td>
</tr>
<tr>
<td>Mean age ± SD, y</td>
</tr>
<tr>
<td>Age group, y</td>
</tr>
<tr>
<td>2 to less than 16, n (%)</td>
</tr>
<tr>
<td>16 or older, n (%)</td>
</tr>
<tr>
<td>Male/female, n</td>
</tr>
<tr>
<td>Race (White/Black/Asian), n</td>
</tr>
<tr>
<td>Chelation-naive, n (%)</td>
</tr>
<tr>
<td>Previous iron chelation therapy, n (%)</td>
</tr>
<tr>
<td>DFO monotherapy</td>
</tr>
<tr>
<td>DFO + deferiprone combination</td>
</tr>
<tr>
<td>Mean duration of previous iron chelation therapy ± SD, y</td>
</tr>
<tr>
<td>Mean duration of transfusion history ± SD, y</td>
</tr>
<tr>
<td>Mean no. of transfusion sessions in the year before study entry ± SD</td>
</tr>
<tr>
<td>Mean total volume red blood cells transfused in the year before study entry ± SD, mL/kg</td>
</tr>
<tr>
<td>Median baseline serum ferritin (range), ng/mL</td>
</tr>
</tbody>
</table>

Lee et al., Blood 116: 2448-2454 (2010)
Iron Overload and Iron Chelation in Patients with Aplastic Anemia

Median serum ferritin at baseline and at 1 year of deferasirox treatment

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

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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• Iron chelation

• Prophylaxis and treatment of infection

• Hematopoietic growth factors
Response and Survival after immunosuppressive treatment of AA

Improved survival in SAA in the past two decades

Which factors are responsible for improved survival in non-responders?

Valdez et al., Clinical Infectious Diseases: 726-735 (2011)
Changing pattern of infections in SAA in the past two decades

Frequency of infections in patients with SAA

Organisms identified in blood cultures obtained from patients with SAA

Valdez et al., Clinical Infectious Diseases: 726-735 (2011)
Meta-analysis: Antibiotic prophylaxis reduces mortality in afebrile neutropenic patients (52 randomized trials)

Fluoroquinolones vs. Placebo:
RR 0.52 (95% CI: 0.35-0.77)

TMP-SMZ vs. Placebo:
RR 0.71 (95% CI: 0.49-1.02)

Other systemic vs. Placebo:
RR 0.95 (95% CI: 0.63-1.45)

Non-adsorbable vs. Placebo:
RR 0.64 (95% CI: 0.44-0.84)

Total
RR 0.67 (95% CI: 0.55-0.81)

### 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>1.00 (0.00–0.87)</td>
<td>25.80</td>
<td>0.05 (0.00–0.87)</td>
</tr>
<tr>
<td>Karp et al., 1987 (16)</td>
<td>6/35</td>
<td>3/33</td>
<td>8.31 (0.51–6.93)</td>
<td>8.31</td>
<td>1.89 (0.51–6.93)</td>
</tr>
<tr>
<td>Schroeder et al., 1992 (22)</td>
<td>0/40</td>
<td>2/35</td>
<td>7.16 (0.01–3.54)</td>
<td>7.16</td>
<td>0.18 (0.01–3.54)</td>
</tr>
<tr>
<td>Talbot et al., 1993 (24)</td>
<td>1/62</td>
<td>2/57</td>
<td>5.61 (0.04–4.93)</td>
<td>5.61</td>
<td>0.46 (0.04–4.93)</td>
</tr>
<tr>
<td>Moreau et al., 1995 (94)</td>
<td>0/44</td>
<td>0/44</td>
<td>1.00 (0.00–0.87)</td>
<td>0/44</td>
<td>Not estimable</td>
</tr>
<tr>
<td>Carlson et al., 1997 (13)</td>
<td>0/45</td>
<td>0/45</td>
<td>1.00 (0.00–0.87)</td>
<td>0/45</td>
<td>Not estimable</td>
</tr>
<tr>
<td>Thomas et al., 2000 (25)</td>
<td>5/99</td>
<td>5/52</td>
<td>17.64 (0.16–1.73)</td>
<td>17.64</td>
<td>0.53 (0.16–1.73)</td>
</tr>
<tr>
<td>Nenova et al., 2001 (20)</td>
<td>0/36</td>
<td>5/34</td>
<td>15.21 (0.09–1.50)</td>
<td>15.21</td>
<td>0.09 (0.00–1.50)</td>
</tr>
<tr>
<td>Tjan-Heijnen et al., 2001 (26)</td>
<td>0/82</td>
<td>5/79</td>
<td>15.07 (0.09–1.56)</td>
<td>15.07</td>
<td>0.09 (0.00–1.56)</td>
</tr>
<tr>
<td>Lee et al., 2002 (17)</td>
<td>2/46</td>
<td>2/49</td>
<td>5.21 (1.07–7.25)</td>
<td>5.21</td>
<td>1.07 (1.07–7.25)</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>542</td>
<td>480</td>
<td>100.00 (0.38–0.69)</td>
<td>100.00</td>
<td>0.38 (0.21–0.69)</td>
</tr>
</tbody>
</table>

Total events: 14 (quinolones), 33 (placebo)
Test for heterogeneity: chi-square = 11.41 (P = 0.12), I^2 = 38.6%
Test for overall effect: Z = 3.20 (P = 0.001)

Metaanalysis:
Antifungal prophylaxis in neutropenic patients after chemotherapy
(64 randomized trials)

Fungal related mortality

- 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. Ampho B 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

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)
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

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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
## Hematopoietic Growth factors in AA

Overall mortality comparing patients treated with IS +/- HGF at 100 days, one year and five years

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>HGF n/N</th>
<th>Control n/N</th>
<th>RR (fixed) 95% CI</th>
<th>Weight %</th>
<th>RR (fixed) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>01 Overall mortality 100 days</td>
<td>0/19</td>
<td>1/19</td>
<td>18.24</td>
<td>0.93 (0.01, 7.70)</td>
<td></td>
</tr>
<tr>
<td>Shao 1998</td>
<td>1/63</td>
<td>0/63</td>
<td>5.26</td>
<td>2.82 (0.12, 68.82)</td>
<td></td>
</tr>
<tr>
<td>Kojima 2000</td>
<td>3/53</td>
<td>4/53</td>
<td>50.47</td>
<td>0.69 (0.16, 2.94)</td>
<td></td>
</tr>
<tr>
<td>Gluckman 2002</td>
<td>0/30</td>
<td>2/49</td>
<td>18.92</td>
<td>2.35 (0.42, 13.25)</td>
<td></td>
</tr>
<tr>
<td>Zheng 2006</td>
<td>2/48</td>
<td>0/47</td>
<td>6.13</td>
<td>4.90 (0.24, 99.38)</td>
<td></td>
</tr>
<tr>
<td>Teramura 2007</td>
<td>183</td>
<td>183</td>
<td>100.00</td>
<td>1.83 (0.55, 6.38)</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>2</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total events: 9 (HGF), 7 (Control)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Test for heterogeneity: Chi² = 2.88, df = 4 (p=0.58), I² = 0%</td>
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<tr>
<td>Test for overall effect: Z = 0.65 (p=0.52)</td>
<td></td>
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</tr>
<tr>
<td>02 Overall mortality 1 year</td>
<td>2/13</td>
<td>4/14</td>
<td>20.84</td>
<td>0.54 (0.12, 2.46)</td>
<td></td>
</tr>
<tr>
<td>Gordon-Smith 1991</td>
<td>4/19</td>
<td>10/19</td>
<td>54.11</td>
<td>0.40 (0.15, 1.25)</td>
<td></td>
</tr>
<tr>
<td>She 1998</td>
<td>2/30</td>
<td>0/30</td>
<td>2.71</td>
<td>5.00 (0.25, 99.95)</td>
<td></td>
</tr>
<tr>
<td>Gluckman 2002</td>
<td>5/60</td>
<td>4/60</td>
<td>16.87</td>
<td>1.96 (0.57, 6.72)</td>
<td></td>
</tr>
<tr>
<td>Zheng 2006</td>
<td>2/48</td>
<td>1/47</td>
<td>5.47</td>
<td>1.90 (0.18, 20.88)</td>
<td></td>
</tr>
<tr>
<td>Teramura 2007</td>
<td>140</td>
<td>157</td>
<td>100.00</td>
<td>0.90 (0.50, 1.63)</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>19</td>
<td>19</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total events: 15 (HGF), 19 (Control)</td>
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<tr>
<td>Test for heterogeneity: Chi² = 6.33, df = 4 (p=0.18), I² = 36.8%</td>
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<tr>
<td>Test for overall effect: Z = 0.34 (p=0.73)</td>
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<tr>
<td>03 Overall mortality 5 years</td>
<td>13/53</td>
<td>13/49</td>
<td>50.82</td>
<td>0.92 (0.48, 1.79)</td>
<td></td>
</tr>
<tr>
<td>Gluckman 2002</td>
<td>6/30</td>
<td>9/47</td>
<td>26.38</td>
<td>1.04 (0.41, 2.64)</td>
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</tr>
<tr>
<td>Zheng 2006</td>
<td>4/48</td>
<td>6/47</td>
<td>22.84</td>
<td>0.65 (0.29, 2.17)</td>
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<tr>
<td>Teramura 2007</td>
<td>131</td>
<td>143</td>
<td>100.00</td>
<td>0.86 (0.65, 1.14)</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>23</td>
<td>28</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Total events: 23 (HGF), 28 (Control)</td>
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<tr>
<td>Test for heterogeneity: Chi² = 6.33, df = 2 (p=0.83), I² = 0%</td>
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<tr>
<td>Test for overall effect: Z = 0.45 (p=0.66)</td>
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</tbody>
</table>

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 10^9/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 G-CSF as single agent for prevention of infection in neutropenic patients.
Supportive Therapy of AA

Thank you for your attention!