Granulocyte transfusion

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Introduction

• 13-60% HSCT recipients develop bacteremia, mortality 3-27%

*Pseudomonas* bacteremia 36-67% mortality

• 2% - 49% patients with hematological malignancies and HSCT develop IFI, mortality up to 70%

• The number of neutrophils correlates with the incidence and the outcome of infections
History

“THE EFFECT OF LEUKOCYTIC CREAM INJECTIONS IN THE TREATMENT OF THE NEUTROPENIAS.”

M. STRUMIA, BY MAX M.D.
American Journal of the Medical Sciences, 1934
Functional studies of transfused granulocytes

• In vitro: evidence by laboratory testing that donated granulocytes are functional

• In neutropenic dogs the transfused cells migrated to the areas of infection

• Successful migration of neutrophils to inflammation sites could be observed in patients

Rex 1995, Bashir Tr Med 03, Bashir BJH 08, Brecher 1953, Adkins Tr 1997
First interest 70s-80s

- Metaanalysis
- 8 RCT GCT in neutropenic patients
- Possible/definitive infections

**Overall mortality**

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Transfusion</th>
<th>Control</th>
<th>Risk Ratio M-H,Random,95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H,Random,95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bow 1984</td>
<td>5/13</td>
<td>4/11</td>
<td>1.06 [0.37, 3.00]</td>
<td>19.2 %</td>
<td>1.06 [0.37, 3.00]</td>
</tr>
<tr>
<td>Herzig 1977</td>
<td>1/13</td>
<td>3/14</td>
<td>0.36 [0.04, 3.03]</td>
<td>7.7 %</td>
<td>0.36 [0.04, 3.03]</td>
</tr>
<tr>
<td>Higby 1975</td>
<td>2/17</td>
<td>14/19</td>
<td>0.16 [0.04, 0.60]</td>
<td>14.8 %</td>
<td>0.16 [0.04, 0.60]</td>
</tr>
<tr>
<td>Scali 1978</td>
<td>0/13</td>
<td>1/12</td>
<td>0.31 [0.01, 6.94]</td>
<td>4.1 %</td>
<td>0.31 [0.01, 6.94]</td>
</tr>
<tr>
<td>Vogler 1977</td>
<td>7/17</td>
<td>9/13</td>
<td>0.59 [0.30, 1.17]</td>
<td>26.3 %</td>
<td>0.59 [0.30, 1.17]</td>
</tr>
<tr>
<td>Winston 1982a</td>
<td>18/48</td>
<td>13/47</td>
<td>1.36 [0.75, 2.44]</td>
<td>28.0 %</td>
<td>1.36 [0.75, 2.44]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>121</strong></td>
<td><strong>116</strong></td>
<td>0.64 [0.33, 1.26]</td>
<td><strong>100.0 %</strong></td>
<td>0.64 [0.33, 1.26]</td>
</tr>
</tbody>
</table>
### Metaanalysis of RCT on GCT in neutropenic patients

**Comparison 2. Sub group mortality analysis**

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Subgroup analysis for studies transfusing &lt; and &gt; 1x10E10 granulocytes (at days 20 - 22, except Winston)</td>
<td>6</td>
<td>240</td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>0.63 [0.32, 1.24]</td>
</tr>
<tr>
<td>1.1 granulocytes &gt; 1 x10E10</td>
<td>4</td>
<td>121</td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>0.37 [0.17, 0.82]</td>
</tr>
<tr>
<td>1.2 granulocytes &lt; 1x10E10</td>
<td>2</td>
<td>119</td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>1.28 [0.76, 2.13]</td>
</tr>
</tbody>
</table>

Stanworth Cochrane review 2005
WBC production:
Unstimulated donor

$0.2 - 0.8 \times 10^{10}$
1% of WBC production of healthy person with bacterial infection

$0.2 \times 10^{10}$ to $0.8 \times 10^{10}$

$10^{11} - 10^{12}$
WBC production:
Steroid-stimulated donor

$2 \times 10^{10}$

$0.2 - 0.8 \times 10^{10}$

$10^{11} - 10^{12}$
WBC production: GCSF-stimulated donor

- 0.2 - 0.8 \times 10^{10}
- 2 \times 10^{10}
- 4 - 8 \times 10^{10}
Stimulation with GCSF

- Increases yield of transfusion
- Prolonged half-life of the cells transfused
- Improves cellular activities of donor neutrophils: motility, killing capacity, respiratory burst
- Upregulates the expression of genes for multiple Toll-like receptors and heightened response against microbes, increasing the antimicrobial activity of the transfused donor granulocytes

Leavey Blood 98; Maianski Blood 02; Van de Wetering 07, Drewniak Blood 10, Strauss Br J Hem 12
How long does the response last?

Filled symbols and the solid line represent the median
Open symbols and dashed lines the lower (25th) and upper (75th) quartile
So,…

• Available donors are needed to maintain regular transfusions, ABO compatible  
  - median delay between diagnosis and GCT was 3 days in unrelated donors  
  5 days in family donors (p=0.01)  

  Hubel Tr 2002

• Donors should be pre-treated with GCSF and steroids

• Logistical limitations
80s-90s

• Benefit – controversial
• New antibiotics
• Donors safety issues
  (and recipients…)

Less interest to GCT

BUT:

Still high mortality
Resistant infections
Back to the future...
Retrospective and prospective studies after 90s

- Indications: bacterial/fungal; definitive/probable/possible
- Patients: children/adults
- Underlying disease: HSCT/ hematological malignancies/severe aplastic anemia/ CGD
- Different protocols to obtain and provide GCT, dosage and regimen
Retrospective and prospective studies after 90s (summary of 27 studies)

<table>
<thead>
<tr>
<th>Endpoints</th>
<th>All infections</th>
<th>Bacterial infections</th>
<th>Fungal infections</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clearance of infection</td>
<td>33% - 92%</td>
<td>64%</td>
<td>30%-100%</td>
</tr>
<tr>
<td>Survival at 4 weeks</td>
<td>50% - 86%</td>
<td>54% - 92%</td>
<td>6%-87%</td>
</tr>
<tr>
<td>Survival at 3 months</td>
<td>30% - 70%</td>
<td>79% - 84%</td>
<td>25% - 66%</td>
</tr>
<tr>
<td>Survival at 6 months</td>
<td>28%-66%</td>
<td>84%</td>
<td>52%</td>
</tr>
</tbody>
</table>
Efficacy of GCT from related and unrelated donors: case control study

- 2 prospective phase I and II studies
- matched those with patients who received no GT
- 74 neutropenic patients
- documented invasive fungal or bacterial infections
- GCT from either community donors or family members

Overall survival to Day 180
Efficacy of GCT from related and unrelated donors: case control study

- Unrelated granulocyte donors
- Related granulocyte donors
- Control patients

Progressive or fatal infections (%)

<table>
<thead>
<tr>
<th>Type of infection</th>
<th>Unrelated (N)</th>
<th>Related (N)</th>
<th>Control (N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mold</td>
<td>90</td>
<td>75</td>
<td>50</td>
</tr>
<tr>
<td>Yeast</td>
<td>60</td>
<td>50</td>
<td>40</td>
</tr>
<tr>
<td>Bacterial</td>
<td>30</td>
<td>25</td>
<td>20</td>
</tr>
</tbody>
</table>

P = 0.04
Efficacy of GCT from related and unrelated donors: case control study

Higher rate of grade IV GvHD

<table>
<thead>
<tr>
<th>GVHD grading</th>
<th>Patients with related granulocyte donors</th>
<th>Patients with unrelated granulocyte donors</th>
<th>Control patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients evaluable</td>
<td>19</td>
<td>13</td>
<td>39</td>
</tr>
<tr>
<td>0 (%)</td>
<td>10 (53)</td>
<td>7 (54)</td>
<td>17 (44)</td>
</tr>
<tr>
<td>I (%)</td>
<td>0</td>
<td>0</td>
<td>2 (5)</td>
</tr>
<tr>
<td>II (%)</td>
<td>3 (16)</td>
<td>0</td>
<td>11 (28)</td>
</tr>
<tr>
<td>III (%)</td>
<td>6 (32)</td>
<td>3 (23)</td>
<td>8 (21)</td>
</tr>
<tr>
<td>IV (%)</td>
<td>0</td>
<td>3 (23)</td>
<td>1 (3)</td>
</tr>
</tbody>
</table>

\[ p = 0.044 \]

Despite irradiation of the granulocyte concentrate

Hübel Tr 2002
To summarize (1):

1) Early studies: inconsistent results
   ➢ higher doses may by beneficial

2) Later non randomized studies showed
   variable response
Can we predict who will benefit from granulocyte transfusions?
What can predict the failure of GCT?

1) Neutrophil recovery
   - The only factor which correlated with favorable response
   - In multivariate analysis: significant influence on survival from severe infections, invasive aspergillosis, invasive candidiasis
What can predict the failure of GCT?

2) Bad performance status

Survival is extremely poor in cases of:

- Septic shock
- ICU (OR 13.6)
- Comorbidities (OR 13.5)
- Multiorgan dysfunction

![Graph showing survival probability over infection-related survival days](image)
What can predict the failure of GCT?

3) Other risk factors:
- Relapse or refractory diseases
- HSCT or neutrophil dysfunction vs. chemotherapy
- Presence of GvHD or VOD
- Pneumonia, multiple infection sites
- Prolonged, disseminated, non-albicans candidemia
- Late administration

Granulocyte transfusions in fungal infections
Bacterial vs. fungal pathogens

![Bar chart comparing bacterial and fungal infections across different studies and time points.](image)

- **Mousset 05 day 30**: 92% bacterial, 78% fungal
- **Seidel 08 day 28**: 90% bacterial, 81% fungal
- **Seidel 09 day 28**: 89% bacterial, 81% fungal
- **Peters 99 day 100**: 51% bacterial, 54% fungal
- **Seidel 08 day 100**: 82% bacterial, 79% fungal
- **Seidel 09 day 100**: 66% bacterial, 65% fungal

*P<0.05
GCT: efficacy in treating fungal infections in neutropenic patients following HSCT

Retrospective study
87 patients during the first 100 days following bone marrow transplantation; 50 received granulocytes in addition to appropriate antifungal agents
GCT in hematologic malignancy patients with invasive aspergillosis

- Retrospective chart review at the MD Anderson Cancer Center
- 1993 - 2010
- Patients with HM (including HSCT) and neutropenia for ≥14 days
- Diagnosis of a proven or probable invasive aspergillosis (IA)
**GCT in hematologic malignancy patients with IA**

- 128 HM patients
- Demographic, clinical, therapeutic characteristics - no significant differences

<table>
<thead>
<tr>
<th></th>
<th>GCT n=53 (41%)</th>
<th>No GCT n=75 (59%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allogeneic HSCT</td>
<td>6/9 (67%)</td>
<td>18/18 (100%)</td>
<td>0.029</td>
</tr>
<tr>
<td>Invasive pulmonary</td>
<td>32 (60%)</td>
<td>62 (83%)</td>
<td>0.005</td>
</tr>
<tr>
<td>infection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Localized infection</td>
<td>14 (26%)</td>
<td>6 (8%)</td>
<td>0.005</td>
</tr>
</tbody>
</table>

Raad Ann Onc 2013
GCT in hematologic malignancy patients with IA

Patients who received GCT:

univariate analysis, invasive pulmonary aspergillosis:

- less likely to respond to antifungal therapy \( (p = 0.03) \)
- more likely to die of IA \( (P = 0.009) \)

multivariate competing risk analysis, patients with IA:

- more likely to die of IA \( (P = 0.011) \)
GCT in hematologic malignancy patients with IA

IA-related death was associated with:

- the number of GCT given \( (P = 0.018) \)
- the early initiation of GTX within 7 days after starting antifungal therapy \( (P = 0.001) \)

53% developed a pulmonary reaction
To summarize (2):

1) Early studies: inconsistent results
   - higher doses may by beneficial

2) Later non randomized studies variable response, in fungal infections less than in bacterial infections

Conclusion: RCT is needed
Randomized phase III study of granulocyte transfusions in neutropenic patients

- Patients: mainly leukemia (87%), including HSCT
- 1999 and 2005
- Inclusion criteria:
  - Malignancy/aplasia
  - Febrile neutropenia (anticipated duration of aplasia >5 more days) and
  - Pulmonary infiltrates or
  - Soft tissue infiltration or
  - History of proven IFI and anticipated duration of neutropenia >10 days
Randomized phase III study of granulocyte transfusions in neutropenic patients

28-day survival

- **All episodes**: 84% (GCT) vs 82% (no GCT)
- **Fungal infections**: 81% (GCT) vs 78% (no GCT)
- **Bacterial/unknown infections**: 90% (GCT) vs 100% (no GCT)

Seidel BMT 08
Randomized phase III study of granulocyte transfusions in neutropenic patients

100-day survival

- All episodes (n=72): 69% GCT, 72% no GCT
- Fungal infections (n=55): 66% GCT, 71% no GCT
- Bacterial/unknown infections (n): 79% GCT, 75% no GCT

Seidel BMT 2008
Randomized phase III study of granulocyte transfusions in neutropenic patients: limitations

- Lag since randomization until GCT
- Insufficient dose and regimen
- “healthy cohort” bias
- 1/3 randomized with ANC > 500 cells/mm$^3$, but rapidly decreasing

- No increased rate of GVHD
Randomized phase III study of granulocyte transfusions in neutropenic patients

Problems with patients recruitment:

• Ten centers participated in the trial;
• Only five recruited patients
• 74 patients = <50% of the expected sample size
• Dramatic decrease in the recruitment rate (from 15 in 2001 to 2 in 2005)

The study was closed prematurely
Prophylactic GCT
Granulocyte transfusions for preventing infections in patients with neutropenia or neutrophil dysfunction

- 10 prospective clinical trials met inclusion criteria (8 from US, one from Spain, one from UK)
- up to October 2008
- all trials were conducted prior to 1987 with the exception of one trial from 2006
- control arm received no prophylactic therapy except in one trial in which the control group received specific prophylactic antibiotics
### Overall Mortality

#### Analysis 1.1. Comparison 1 Mortality - overall, Outcome 1 Overall mortality.

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

**Comparison:** 1 Mortality - overall

**Outcome:** 1 Overall mortality

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Granulocytes n/N</th>
<th>No granulocytes n/N</th>
<th>Risk Ratio M-H,Random,95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H,Random,95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cliff 1978</td>
<td>0/41</td>
<td>1/45</td>
<td>0.8 %</td>
<td>0.37 [ 0.02, 8.72 ]</td>
<td></td>
</tr>
<tr>
<td>Ford 1982</td>
<td>3/13</td>
<td>2/11</td>
<td>3.1 %</td>
<td>1.27 [ 0.26, 6.28 ]</td>
<td></td>
</tr>
<tr>
<td>Gomez-Villagran 1984</td>
<td>2/19</td>
<td>6/16</td>
<td>3.7 %</td>
<td>0.28 [ 0.07, 1.20 ]</td>
<td></td>
</tr>
<tr>
<td>Mannoni 1979</td>
<td>0/20</td>
<td>4/26</td>
<td>1.0 %</td>
<td>0.14 [ 0.01, 2.51 ]</td>
<td></td>
</tr>
<tr>
<td>Oza 2006</td>
<td>2/53</td>
<td>5/98</td>
<td>3.0 %</td>
<td>0.74 [ 0.15, 3.68 ]</td>
<td></td>
</tr>
<tr>
<td>Petersen 1987</td>
<td>2/67</td>
<td>11/47</td>
<td>19.3 %</td>
<td>1.03 [ 0.55, 1.95 ]</td>
<td></td>
</tr>
<tr>
<td>Schiffer 1979</td>
<td>0/12</td>
<td>2/10</td>
<td>0.9 %</td>
<td>0.17 [ 0.01, 3.16 ]</td>
<td></td>
</tr>
<tr>
<td>Strauss 1981</td>
<td>12/54</td>
<td>6/48</td>
<td>9.7 %</td>
<td>1.78 [ 0.72, 4.37 ]</td>
<td></td>
</tr>
<tr>
<td>Sutton 1982</td>
<td>9/29</td>
<td>14/38</td>
<td>16.7 %</td>
<td>0.84 [ 0.43, 1.67 ]</td>
<td></td>
</tr>
<tr>
<td>Winston 1980</td>
<td>13/19</td>
<td>13/19</td>
<td>41.9 %</td>
<td>1.00 [ 0.65, 1.54 ]</td>
<td></td>
</tr>
</tbody>
</table>

**Total (95% CI):**

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Granulocytes n/N</th>
<th>No granulocytes n/N</th>
<th>Risk Ratio M-H,Random,95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H,Random,95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total</strong></td>
<td><strong>347</strong></td>
<td><strong>358</strong></td>
<td><strong>100.0 %</strong></td>
<td><strong>0.94 [ 0.71, 1.25 ]</strong></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 62 (Granulocytes), 64 (No granulocytes)

Heterogeneity: Tau² = 0.0; Chi² = 8.63, df = 9 (P = 0.47); I² = 0.0%

Test for overall effect: Z = 0.41 (P = 0.68)

Favours treatment | Favours control

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Massey The Cochrane Review 09
Overall Mortality, excluding low dose studies

Analysis 1.2. Comparison 1 Mortality - overall, Outcome 2 Mortality - overall, excluding low dose studies.

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

Comparison: 1 Mortality - overall

Outcome: 2 Mortality - overall, excluding low dose studies

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Treatment n/V</th>
<th>Control n/V</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clift 1978</td>
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<td></td>
<td>1.1 %</td>
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<td>Petersen 1987</td>
<td>21/87</td>
<td>11/47</td>
<td></td>
<td>26.5 %</td>
<td>1.03 [0.55, 1.95]</td>
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<td>Schiffer 1979</td>
<td>0/12</td>
<td>2/10</td>
<td></td>
<td>1.3 %</td>
<td>0.17 [0.01, 3.16]</td>
</tr>
<tr>
<td>Winston 1980</td>
<td>13/19</td>
<td>13/19</td>
<td></td>
<td>56.1 %</td>
<td>1.00 [0.65, 1.54]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>264</strong></td>
<td><strong>272</strong></td>
<td></td>
<td><strong>100.0 %</strong></td>
<td><strong>0.89 [0.64, 1.24]</strong></td>
</tr>
</tbody>
</table>

Total events: 41 (Treatment), 44 (Control)
Heterogeneity: Tau² = 0.00; Chi² = 7.05, df = 7 (P = 0.42); I² = 1%
Test for overall effect: Z = 0.71 (P = 0.48)
Cochrane Review: Conclusions

• prophylactic granulocyte transfusions given to neutropenic patients at a dose of at least $1 \times 10^{10}$ do not decrease the risk of overall mortality but may possibly reduce the risk of mortality from infection and reduce the number of infective episodes;

• High rate of adverse reactions
  - Fever
  - TA-GVHD (one death)
  - HLA-alloimmunization
  - Pulmonary reactions
To summarize (3):

1) Early studies: inconsistent results
   - higher doses may be beneficial

2) Later non-RCT studies: broad range of success
   - fungal << bacterial

3) RCT - no benefit in survival
   - but protocol can be improved

4) Prophylactic studies - overall mortality was not reduced
Adverse events during GCT

• Up to 30% develop reactions
• Severity: usually mild
  – 8-45% fever
  – 6-30% chills
  – 1-5% rashes
  – 2-6.5% hypotension
• 7% severe GTX-associated toxicity that led to discontinuation of GTX

Dignani Leuk 97, Hubel Tr 02, Seidel JPHO 09, Kim Cytoth 11, Safdar Acta Haem 2014, Stroncek Tr 96, Lehrnbecher Fr Onc 13, Peters BJH 99, Bux Vox Sang 03
Adverse events during GCT

• Transmission of CMV (fatal disease reported)

• Transmission of West Nile

• Transmission of Toxoplasmosis
Case presentation

• 16 years old girl
• Severe aplastic anemia
• Post rabbit ATG, alemtuzumab, prednisolone
• On admission, CT of the lungs revealed nodules in the right upper, right middle, and left lower lobes
• Worsening on voriconazole treatment, switched to liposomal ampho + caspofungin
• GCT initiated
Increasing dyspnea and hypoxia, revealed increasing size of existing nodules, and new right lower and middle lobe consolidation and left lower lobe airspace disease.
The possible reason?
Respiratory reactions during GCT

- Frequency: 0-53%
- Severity: mild - severe
- Clinical spectrum: shortness of breath, dyspnea, chest tightness, acral cyanosis
- Hypoxia, severe bronchospasm
- X ray changes
- Increase in ventilator support
- Rare: pulmonary edema, heart failure (rapid transfusions), severe respiratory complications (Kim 2011: 10% acute respiratory failure and/or massive hemoptysis)

Dignani Leuk 97, Grigull SCC 06, Quillen Haemat 09, Seidel, Kim Cytother 11, Raad ann Onc 13, Diaz PHO 14, HubelTr 02, Wang Plos1 14
The possible reason?

- Worsening current infection (ineffective treatment)
- Presence of another infection (Nocardia, CMV)
- Trafficking of neutrophils to the site of infection
- Alloimmunization
12-80% of granulocyte transfusion recipients develop antibodies to HLA class I / HNA antigens
Alloimmunization

- Lower response to GCT
- Shorter $T_{1/2}$ of transfused granulocytes (0.3 hr vs. 5.6 hr in controls)
- Impaired trafficking to sites of infection
- Predispose to post-transfusion reactions
- Engraftment rejection (alloimmunization to HLA)
- Refractoriness to platelet transfusion after HSCT, especially cord blood transplantation

- But: some studies did not show correlation between presence of antibodies and post-transfusion PMN recovery or incidence of transfusion reaction

Stroncek Tr 96, Heim Tr 11, McCullough Tr 11, Sachs Blood 11, Strauss BJH 12, Vamvakas, Ungerleider Transf 79
Caspofungin and pulmonary reactions post GCT

Mechanism of action of caspofungin
Cell re-modelling: Increase exposure of 1,3-glucan on the *Aspergillus* hyphal cell surface

(Staining with a immunofluorescent monoclonal antibody that recognizes - 1,3-glucan)
Donors' side effects following GCSF and steroids

- Bone pain mild to moderate (90%)
- Headache (33%)  
- Myalgia  
- Itching may be severe  
- Insomnia (~30%), restlessness  
- Sweating  
- Nausea  
- Rare: anaphylactoid reaction, disseminated intravascular coagulopathy and shock, pulmonary hemorrhage, splenic rupture, iritis, cardiac ischemia, and gouty arthritis

However, only 5% would not agree to donate granulocytes again

Cesaro SCC 03, De la Rubia Haemat 08, Peters Vox Sang 09, Quillen Transf 09, Adkins J Clin Oncol 98, Bux Vox Sang 03, Kopp JCO 07, Kikuta Vox Sang 06
Donors` side effects

Concerns

• Posterior subcapsular cataract (PSC)
• Malignancies
• Thrombophilia

Ethical issues

Ghodsi Tr 01, Burch Tr 05, Clayton Tr 11, Bennett BJH 06, Confer BJH 07, Anderlini COH 09, Quillen Tr 09, Falanga Blood 99, Canales JHSR 02, Kikuta Vox Sang 06, Cavallaro BMT 00, Hill JACC 2005.
To summarize (4):

1) Early studies: inconsistent results
   - higher doses may be beneficial

2) Later non-RCT studies: broad range of success
   - fungal << bacterial

3) RCT - no benefit in survival
   - but protocol can be improved

4) Prophylactic studies - overall mortality was not reduced

5) Side effects in recipients, rare - severe

6) Side effects in donors
Criteria to provide GCT

1) Patients with severe neutropenia (ANC <0.5 x $10^9$/L) due to congenital or acquired bone marrow failure syndromes or congenital disorder of neutrophil function

2) Proven or highly probable fungal or bacterial infection unresponsive to appropriate antimicrobial therapy

3) Under active treatment in an attempt to achieve disease remission

4) Neutrophil recovery is anticipated
The RING Study
(Resolving Infection in Neutropenia With Granulocytes)

Safety and Effectiveness of High Dose Granulocyte Transfusions in Resolving Infection in People With Neutropenia

Randomized Single Blind
(Outcomes Assessor)

Endpoint: Safety/Efficacy