



YEDİTEPE ÜNİVERSİTESİ



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# KÖK HÜCRE NAKLİNDE AKILCI SEÇİMLER – ASBMT 2018

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Yeditepe Üniversitesi İhtisas Hastanesi

Hematoloji BD, Kemik İliği Nakli Merkezi

Kadıköy/İstanbul



*An initiative of the ABIM Foundation*

American Society for Blood and Marrow Transplantation  
and the Canadian Blood and Marrow Transplant Group



## Five Things Physicians and Patients Should Question

1

**Don't routinely use peripheral blood stem cells for patients with aplastic anemia when a suitable bone marrow donor is available due to a higher risk of graft-versus-host disease.**

While faster engraftment with filgrastim-mobilized peripheral blood stem cells results in quicker recovery of peripheral blood counts compared to bone marrow in patients with aplastic anemia, the higher rate of graft-versus-host disease may be detrimental.

2

**Don't use greater than 2 mg/kg/day of methylprednisolone (or equivalent) for the initial treatment of graft-versus-host disease.**

Published studies have shown no advantage to using methylprednisolone-equivalent doses higher than 2 mg/kg/day in acute graft-versus-host disease. In addition, using higher doses increases risks of corticosteroid related toxicity. Furthermore, at least in patients with grade I-II acute graft-versus-host disease, initial therapy with lower-dose corticosteroids at 1 mg/kg/day may be equivalent.

3

**Don't routinely use two cord blood units for standard umbilical cord blood transplantation when a single unit of adequate size is available, recognizing that higher cell doses are preferred when using units with greater HLA mismatch.**

Randomized trials demonstrate similar clinical outcomes after single-unit and double-unit umbilical cord blood transplantation, including comparable rates of relapse, engraftment failure, overall survival, and transplantation related mortality. Moreover, graft-versus-host disease may be more frequent after double-cord blood transplantation.

4

**Don't routinely use peripheral blood stem cells for matched unrelated donor transplantation using myeloablative conditioning and standard graft-versus-host disease prevention regimens when a suitable bone marrow donor is available.**

Patients undergoing myeloablative matched unrelated donor hematopoietic cell transplantation with standard graft-versus-host disease prophylaxis (calcineurin inhibitor and methotrexate) with a peripheral blood stem cell graft experience more symptomatic chronic graft-versus-host disease than those receiving bone marrow, without affecting relapse rates or overall survival. Peripheral blood stem cells may be considered in cases with substantial recipient/donor size discrepancy, donor preference, and for malignant diseases with high risk for graft failure.

5

**Don't routinely give immunoglobulin replacement to adult hematopoietic cell transplantation recipients in the absence of recurrent infections regardless of the IgG level.**

Meta-analyses of controlled trials conclude that immunoglobulin replacement offers no advantage for infection prevention and overall survival, and may predispose to a higher risk of hepatic sinusoidal obstruction syndrome and venous thromboembolism, and impair the efficacy of post-transplant vaccinations. There may be subsets of patients where prophylactic immunoglobulin replacement may be considered, such as in umbilical cord blood transplant recipients, in children undergoing transplantation for inherited or acquired disorders associated with B-cell deficiency, and in chronic graft-versus-host disease patients with recurrent sino-pulmonary infections.

1

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- ***Aplastik anemi hastalarında, yüksek graft-versus-host hastalığı riski nedeniyle uygun bir kemik iliği vericisi varlığında periferik kök hücrelerini rutin olarak kullanmayın***
  - Aplastik anemi hastalarında kemik iliği ile karşılaştırıldığında filgrastim ile mobilize edilmiş periferik kök hücreler daha hızlı yamanma ve periferik kan tablosunda düzelme ile sonuçlansa da yüksek graft-versus-host hastalığı hızı çok zararlı olabilmektedir.

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*Blood Cells, Molecules and Diseases 55 (2015) 40–47*

**bjh** guideline

## Guidelines for the diagnosis and management of adult aplastic anaemia

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- Edinsel Aplastik Anemi (AA), pansitopeni ve hipoplastik kemik iliği ile karakterize nadir ve heterojen bir hastalık
- 2-3/1.000.000 insidansı (Doğu Asya bölgesinde daha yüksek)
- 70-80% idiopatik, 20-30% ilaç, kimyasallar ve enfeksiyonlar ..
- Ağır aplastik anemide yaşam süresi son 20 yıl içinde uzadı. Bunun temel nedenleri aşağıdaki unsurlarda elde edilen iyileşmeler
  - Kök hücre nakli
  - İmmünsüpresif tedavi
  - Biyolojik ilaçlar
  - Destek tedavileri

## Don't routinely use peripheral blood stem cells for patients with aplastic anemia when a suitable bone marrow donor is available due to a higher risk of graft-versus-host disease.

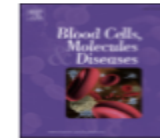
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- Medline: 1971 – 2014 Mart tarihleri arası taranmış
- 224 makaleden – 54 makale dahil edilmiş
- Ek olarak hematoloji textbookları ve hematoloji kongreleri taranmış
- Her elde edilen kanıt, kanıt kriterlerine uygun şekilde skorlanarak öneride bulunulmuş

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**Table 2**

Classification of AA based on the severity.

Moderate or non-severe (NSAA)	Severe	Very severe
<ul style="list-style-type: none"> <li>&gt; Hematopoietic marrow cellularity &lt; 30%</li> <li>&gt; Neutrophils &gt; <math>0.5 \times 10^9/l</math> but &lt; <math>1.0 \times 10^9/l</math></li> <li>or: lack of criteria for severe and very severe</li> </ul>	<ul style="list-style-type: none"> <li>&gt; Hematopoietic marrow cellularity &lt; 30%</li> <li>&gt; At least two of the following conditions:               <ul style="list-style-type: none"> <li>– Neutrophils &lt; <math>0.5 \times 10^9/l</math></li> <li>– Platelets &lt; <math>20 \times 10^9/l</math></li> <li>– Reticulocytes &lt; <math>20 \times 10^9/l^a</math></li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>Like severe but with neutrophils &lt; <math>0.2 \times 10^9/l</math></li> </ul>

<sup>a</sup> If reticulocytes are measured manually. Values should be <  $0.6 \times 10^9/l$  if reticulocytes are measured with automatic coulter since the instrument may over-estimate lower values.

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**Table 1**

Agents reported to be associated with the occurrence of AA.

Drugs
Antibiotics:
chloramphenicol (no evidence for eye drops and tablets), sulphonamide, cotrimoxazole, linezolid
Antirheumatics:
gold salts, penicillamine,
Anti-inflammatory:
indomethacin, phenylbutazone, naproxen, diclofenac, piroxicam, sulfasalazine
Anticonvulsants:
phenytoin, carbamazepine
Thyroid drugs:
carbamazole (neutropenia), thiouracil
Antidepressants:
phenothiazine, dothiepin
Hypoglycemic drugs:
chlorpropamide, tolbutamide
Antimalarials:
chloroquine
Others:
mebendazole, allopurinol, thiazide diuretics
Chemicals
Benzene and other solvents
Pesticides:
organochlorine and organophosphate, pentachlorophenol, DDT and carbamate
Oils and other lubricant agents
Narcotic drugs:
ecstasy, methylene dioxy-methamphetamine (MDMA)
Others:
Exposure to non-drinkable water, to non-sterile needles, farmers in contact with fowls

**Table 3**

Diagnostic work-up of aplastic anemia.

Mandatory tests for the diagnosis of AA
✓ Full blood count with differential count
✓ Reticulocyte count
✓ Peripheral blood film
✓ Liver function tests
✓ Liver virus tests (antibodies and DNA/RNA)
✓ Bone marrow aspirate for morphology, cytogenetics, immunophenotype, Pearl's staining (for intra-cytoplasmic iron)
✓ Bone marrow trephine biopsy with immunostaining for CD34 and CD117
✓ Flow cytometry for PNH clones
✓ Autoantibody screening (anti-nucleus and anti-DNA for SLE detection)
✓ Vitamin B12 and folate serum levels
✓ Fibrinogen and serum ferritin (detection of HLH)
✓ Stool pancreatic elastase, serum pancreatic lipase (for identification of Shwachman Syndrome)
✓ Serum bilirubin and LDH
✓ Chest X-ray
✓ Abdomen US scan and echocardiography (for liver, spleen, lymph node enlargement and malformations)
Mandatory tests for differential diagnosis with constitutional marrow failure syndromes
✓ Chromosomal fragility tests (MMC or DEB). Gold standard for the diagnosis of Fanconi Anemia
✓ TERC mutation analysis (detection of hidden forms of DKC)
✓ TERT mutation analysis (for those who do not respond to IST)
Ancillary tests for the diagnosis of AA
✓ Search for mycobacteria infection (atypical mycobacteria more frequently than TB mycobacteria)
✓ Marrow progenitor assay (not available in all centers)
✓ MRI of vertebral column
Ancillary tests for differential diagnosis with constitutional marrow failure syndromes
✓ TNF2, NHP2, NOP10, DKC1 and cMPL mutation analysis
✓ Shwachman-Diamond Syndrome mutation analysis, telomere length measurement



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### • **HLA-Eş Aile içi AKHN**

- Ağır, çok ağır AA ve transfüzyon bağımlı AA'lerde **Kemik iliği kaynaklı** kök hücre nakli önerilir. (Kanıt derecesi II, Konsensus gücü 8.5, B)
- **Hazırlama rejimi** olarak; ATG 2.5 mg/kg (d-4,-3,-2) + Cy 50 mg/kg (d-5,-4,-3,-2) önerilir. (Kanıt derecesi II, Konsensus gücü 8.4, B)
- **GVHH profilaksisi** olarak; CsA + Mtx (Kanıt derecesi III, Konsensus gücü 8.5, C)

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### • *İmmünsüpresif tedavi*

- HLA – Eş aile içi verici yok ise **ATG + CsA** halen ilk sıra tercih edilmesi gereken tedavi seçeneğidir (Kanıt derecesi II, Konsensus gücü 8.5, B)
- ATG (**At kaynaklı**), CsA 5 mg/kg dozunda en iyi yanıt sonrası 12 ay daha devam edilmeli. Takiben her ay 10% azaltılarak 24 aydan önce olmamak şartıyla kesilmeli (Kanıt derecesi II, Konsensus gücü 7.8, C)

## Don't routinely use peripheral blood stem cells for patients with aplastic anemia when a suitable bone marrow donor is available due to a higher risk of graft-versus-host disease.

While faster engraftment with filgrastim-mobilized peripheral blood stem cells results in quicker recovery of peripheral blood counts compared to bone marrow in patients with aplastic anemia, the higher rate of graft-versus-host disease may be detrimental.



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Blood Cells, Molecules and Diseases 55 (2015) 40–47

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### • **HLA – Eş Akrabadişi KHN**

- IST sonrası relaps eden veya yanıtı olmayan hastalar, eğer 10/10 veya 9/10 akrabadışı donör adayları mevcut ise KHN yapılmalıdır. (Kanıt derecesi II, Konsensus gücü 8.5, B)
- Hazırlama rejimi olarak; Flu 120 mg/m<sup>2</sup> + Cy 120 mg/kg + ATG (d-3,-2) >14 yaş veya çoklu transfüzyon geçmiş olan hastalara ek olarak TBI 2 Gy önerilir (Kanıt derecesi II, Konsensus gücü 8.4, B)
- GVHH profilaksisi olarak; Mtx/CsA önerilir (Kanıt derecesi III, Konsensus gücü 8.5, C)



## Don't routinely use peripheral blood stem cells for patients with aplastic anemia when a suitable bone marrow donor is available due to a higher risk of graft-versus-host disease.

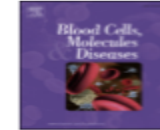
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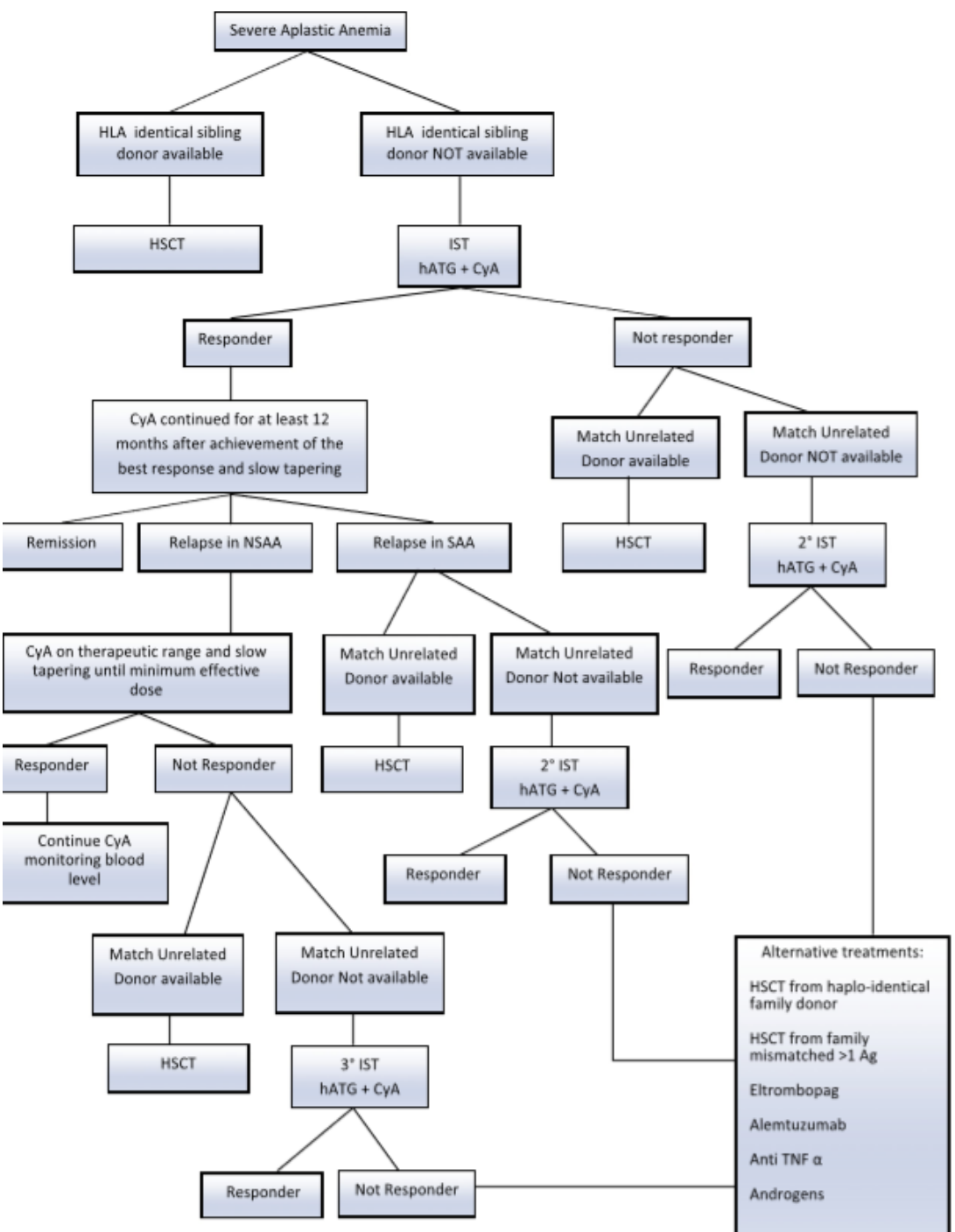
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Piero Farruggia <sup>k,2</sup>, Carlo Dufour <sup>g,\*,2</sup>, Paola Saracco <sup>r,2</sup>

- **HLA-Eş akrabadışı vericisi olmayan ve 2. seri IST'ye refrakter hastalarda önerilen seçenekler**
  - 3. seri IST
  - Aile içi Haploidentik KHN
  - Kordon kanı KHN
  - KHN içermeyen alternatif tedaviler

# Diagnosis and management of acquired aplastic anemia in childhood. Guidelines from the Marrow Failure Study Group of the Pediatric Haemato-Oncology Italian Association (AIEOP)

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Don't routinely use peripheral blood stem cells for patients with aplastic anemia when a suitable bone marrow donor is available due to a higher risk of graft-versus-host disease.

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*Blood Cells, Molecules and Diseases 55 (2015) 40–47*

**bjh** guideline

## Guidelines for the diagnosis and management of adult aplastic anaemia

Sally B. Killick, Writing Group Chair<sup>1</sup> Nick Bown,<sup>2</sup> Jamie Cavenagh,<sup>3</sup> Inderjeet Dokal,<sup>4</sup> Theodora Foukaneli,<sup>5</sup> Anita Hill,<sup>6</sup> Peter Hillmen,<sup>6</sup> Robin Ireland,<sup>7</sup> Austin Kulasekararaj,<sup>7</sup> Ghulam Mufti,<sup>7</sup> John A. Snowden,<sup>8</sup> Sujith Samarasinghe,<sup>9</sup> Anna Wood, BCSH Task Force Member<sup>10</sup> and Judith C. W. Marsh<sup>7</sup> on behalf of the British Society for Standards in Haematology

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- **Tanım, şiddeti ve prezantasyonu için öneriler**
  - AA şiddeti Camitta kriterlerine göre belirlenmelidir (Grade 1C)
  - Çoğu AA hastası idiopatik olsa da dikkatlice ilaç hikayesi alınmalı ve şüpheli bir ilaç var ise kesilmelidir (Grade 1C)



## Don't routinely use peripheral blood stem cells for patients with aplastic anemia when a suitable bone marrow donor is available due to a higher risk of graft-versus-host disease.

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- **Kalıtsal AA için öneriler**

- Fankoni Anemisi (FA) için diepoxybutane maruziyeti sonrası periferik kan lenfositlerinden kromozom kırığı analizi yapılmalıdır (Grade 1B)
- Ek destekler bulgular için detaylı araştırmalar ( aile sorgusu, batın USG vs..) (Grade 1B)

## Don't routinely use peripheral blood stem cells for patients with aplastic anemia when a suitable bone marrow donor is available due to a higher risk of graft-versus-host disease.

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- **IST için öneriler**
  - At kaynaklı ATG + CsA kombinasyonu altın standart ilk seri IST'dir. (Grade 1A)
  - Transfüzyon bağımlı ağır olmayan AA, MSD olmayan veya yaş > 35-50 olan ağır /çok ağır AA hastalarında da ilk seri olarak IST önerilir (Grade 1A)
  - İlk seri ATG'ye yanıtızsız veya relaps eden hastalarda uygun MUD yok ise 2. seri ATG verilebilir (Grade 1A)
  - KHN dışında orta veya yüksek doz Cy kullanımı önerilmez (Grade 1A)

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## **Guidelines for the diagnosis and management of adult aplastic anaemia**

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- **KHN için öneriler**

- KHN adayı olan tüm hastalara tanı anında HLA doku tiplendirmesi yapılmalı ve takiben akraba ve gerekirse akrabadışı tarama başlanmalıdır (Grade 1B)
- Tanı anında hastalar, hazırlama rejimi farklı olacağından MDS ve PNH, toksik etkileri ve kardeş verici seçimi etkileneceğinden kalıtsal AA'ler yönünden dikkatlice ayırıcı tanı yapılmalıdır (Grade 1C)
- KHN morbidite indeksi dökümente edilmelidir (Grade 2B)
- Genç ve erişkin AAA hastalarında ilk seri MSD KHN ilk tercih olmakla birlikte 35-50 yaş arasındaki erişkin hastalar birliktelik gösteren morbiditeler açısından dikkatlice değerlendirilmelidir (Grade 1B)
- Erişkinlerde, Akrabadışı KHN'i ancak bir seri IST yanıtsızlığı sonrası düşünülmelidir (Grade 1B)
- Uygun verici adayı olmayan hastalarda alternatif verici KHN'nin başarısı son zamanda artış gösterse de bu nakil tipinin halen deneysel olduğu unutulmamalı ve ancak deneyimli merkezlerde SAAWP onaylı protokoller ile uygulanmalıdır (Grade 2B)



An initiative of the ABIM Foundation

American Society for Blood and Marrow Transplantation  
and the Canadian Blood and Marrow Transplant Group



## Five Things Physicians and Patients Should Question

1

### **Don't routinely use peripheral blood stem cells for patients with aplastic anemia when a suitable bone marrow donor is available due to a higher risk of graft-versus-host disease.**

While faster engraftment with filgrastim-mobilized peripheral blood stem cells results in quicker recovery of peripheral blood counts compared to bone marrow in patients with aplastic anemia, the higher rate of graft-versus-host disease may be detrimental.

2

### **Don't use greater than 2 mg/kg/day of methylprednisolone (or equivalent) for the initial treatment of graft-versus-host disease.**

Published studies have shown no advantage to using methylprednisolone-equivalent doses higher than 2 mg/kg/day in acute graft-versus-host disease. In addition, using higher doses increases risks of corticosteroid related toxicity. Furthermore, at least in patients with grade I-II acute graft-versus-host disease, initial therapy with lower-dose corticosteroids at 1 mg/kg/day may be equivalent.

3

### **Don't routinely use two cord blood units for standard umbilical cord blood transplantation when a single unit of adequate size is available, recognizing that higher cell doses are preferred when using units with greater HLA mismatch.**

Randomized trials demonstrate similar clinical outcomes after single-unit and double-unit umbilical cord blood transplantation, including comparable rates of relapse, engraftment failure, overall survival, and transplantation related mortality. Moreover, graft-versus-host disease may be more frequent after double-cord blood transplantation.

4

### **Don't routinely use peripheral blood stem cells for matched unrelated donor transplantation using myeloablative conditioning and standard graft-versus-host disease prevention regimens when a suitable bone marrow donor is available.**

Patients undergoing myeloablative matched unrelated donor hematopoietic cell transplantation with standard graft-versus-host disease prophylaxis (calcineurin inhibitor and methotrexate) with a peripheral blood stem cell graft experience more symptomatic chronic graft-versus-host disease than those receiving bone marrow, without affecting relapse rates or overall survival. Peripheral blood stem cells may be considered in cases with substantial recipient/donor size discrepancy, donor preference, and for malignant diseases with high risk for graft failure.

5

### **Don't routinely give immunoglobulin replacement to adult hematopoietic cell transplantation recipients in the absence of recurrent infections regardless of the IgG level.**

Meta-analyses of controlled trials conclude that immunoglobulin replacement offers no advantage for infection prevention and overall survival, and may predispose to a higher risk of hepatic sinusoidal obstruction syndrome and venous thromboembolism, and impair the efficacy of post-transplant vaccinations. There may be subsets of patients where prophylactic immunoglobulin replacement may be considered, such as in umbilical cord blood transplant recipients, in children undergoing transplantation for inherited or acquired disorders associated with B-cell deficiency, and in chronic graft-versus-host disease patients with recurrent sino-pulmonary infections.



2

## Don't use greater than 2 mg/kg/day of methylprednisolone (or equivalent) for the initial treatment of graft-versus-host disease.

Published studies have shown no advantage to using methylprednisolone-equivalent doses higher than 2 mg/kg/day in acute graft-versus-host disease. In addition, using higher doses increases risks of corticosteroid related toxicity. Furthermore, at least in patients with grade I-II acute graft-versus-host disease, initial therapy with lower-dose corticosteroids at 1 mg/kg/day may be equivalent.

- ***Graft-versus-host hastalığı için ilk sıra tedavide 2 mg/kg/gün metilprednizolon'dan (veya eşdeğeri) daha yüksek doz kullanmayın***
  - Yayınlanmış çalışmalar, akut graft-versus-host hastalığı tedavisinde 2 mg/kg/gün metilprednizolon'dan (veya eşdeğeri) daha yüksek dozların avantaj sağlamadığını göstermiştir. Ayrıca, Daha yüksek dozlar steroid ilişkili toksisiteyi arttırmaktadır. Bununla beraber, en azından grade I-II akut GVHH sahip hastalarda başlangıç dozu olarak 1 mg/kg/gün yeterli olabilir

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Published studies have shown no advantage to using methylprednisolone-equivalent doses higher than 2 mg/kg/day in acute graft-versus-host disease. In addition, using higher doses increases risks of corticosteroid related toxicity. Furthermore, at least in patients with grade I-II acute graft-versus-host disease, initial therapy with lower-dose corticosteroids at 1 mg/kg/day may be equivalent.



### NIH Public Access

#### Author Manuscript

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### First and Second-Line Systemic Treatment of Acute Graft-versus-host Disease: Recommendations of the American Society of Blood and Marrow Transplantation

Paul J. Martin<sup>1</sup>, J. Douglas Rizzo<sup>2</sup>, John R. Wingard<sup>3</sup>, Karen Ballen<sup>4</sup>, Peter T. Curtin<sup>5</sup>, Corey Cutler<sup>6</sup>, Mark R. Litzow<sup>7</sup>, Yago Nieto<sup>8</sup>, Bipin N. Sayani<sup>9</sup>, Jeffrey R. Schriber<sup>10</sup>, Paul J. Shaughnessy<sup>11</sup>, Donna A. Wall<sup>12</sup>, and Paul A. Carpenter<sup>1</sup>

- Medline: 1990 – 2011 tarihleri arası akut GVHH tedavisini konu alan makaleler taranmış
- < 10 hasta içeren, olgu sunumları ve ticari olarak elde edilemeyen ilaç kullanılmış makaleler dışlanmış
- Akut GVHH'nda ilk seri tedaviyi inceleyen 13 makale, 2. seri tedaviyi inceleyen 67 makale tespit edilmiş. Kriterleri karşılayan 29 makale değerlendirmeye alınmış

2

## Don't use greater than 2 mg/kg/day of methylprednisolone (or equivalent) for the initial treatment of graft-versus-host disease.

Published studies have shown no advantage to using methylprednisolone-equivalent doses higher than 2 mg/kg/day in acute graft-versus-host disease. In addition, using higher doses increases risks of corticosteroid related toxicity. Furthermore, at least in patients with grade II acute graft-versus-host disease, initial therapy with lower-dose corticosteroids at 1 mg/kg/day may be equivalent.



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## • Akut GVHH ilk seri sistemik tedavisi için öneriler ve sonuçlar

Summary of Studies Evaluating Systemic Agents for Initial Therapy of Acute GVHD \*

Reference	Agent	Phase	No. of patients	Response Assessment	CR Proportion	CR or PR Proportion	6-month Survival
<b>Comparative studies</b>							
[7]	High-dose Pred	3	48				0.74
	Pred		47				0.63
[8]	Low-dose Pred	Retro	347				0.77
	Pred		386				0.69

2

## Don't use greater than 2 mg/kg/day of methylprednisolone (or equivalent) for the initial treatment of graft-versus-host disease.

Published studies have shown no advantage to using methylprednisolone-equivalent doses higher than 2 mg/kg/day in acute graft-versus-host disease. In addition, using higher doses increases risks of corticosteroid related toxicity. Furthermore, at least in patients with grade I-II acute graft-versus-host disease, initial therapy with lower-dose corticosteroids at 1 mg/kg/day may be equivalent.



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### First and Second-Line Systemic Treatment of Acute Graft-versus-host Disease: Recommendations of the American Society of Blood and Marrow Transplantation

Paul J. Martin<sup>1</sup>, J. Douglas Rizzo<sup>2</sup>, John R. Wingard<sup>3</sup>, Karen Ballen<sup>4</sup>, Peter T. Curtin<sup>5</sup>, Corey Cutler<sup>6</sup>, Mark R. Litzow<sup>7</sup>, Yago Nieto<sup>8</sup>, Bipin N. Sayani<sup>9</sup>, Jeffrey R. Schriber<sup>10</sup>, Paul J. Shaughnessy<sup>11</sup>, Donna A. Wall<sup>12</sup>, and Paul A. Carpenter<sup>1</sup>

- **Akut GVHH ilk seri sistemik tedavisi için öneriler ve sonuçlar**
  - Bu iki makale verileri, graft-versus-host hastalığı için ilk sıra tedavide 2.5 mg/kg/gün prednizon'dan (veya eşdeğeri) daha yüksek doz kullanımının bir avantaj getirmediğini ve en azından grade I-II akut GVHH sahip hastalarda başlangıç dozu olarak 1 mg/kg/gün yeterli olabileceğini göstermiştir.
  - Grade III-IV GVHH hastalarında daha düşük dozlarda steroid kullanımı ile ilgili tecrübe yetersizdir.
  - Bu sorulara ışık tutacak prospektik bir çalışma halen devam etmektedir (NCT00929695).



2

## Don't use greater than 2 mg/kg/day of methylprednisolone (or equivalent) for the initial treatment of graft-versus-host disease.

Published studies have shown no advantage to using methylprednisolone-equivalent doses higher than 2 mg/kg/day in acute graft-versus-host disease. In addition, using higher doses increases risks of corticosteroid related toxicity. Furthermore, at least in patients with grade I-II acute graft-versus-host disease, initial therapy with lower-dose corticosteroids at 1 mg/kg/day may be equivalent.

## Low-Dose Prednisone or Methylprednisolone in Treating Patients With Newly Diagnosed Acute Graft-versus-Host Disease

ClinicalTrials.gov Identifier: NCT00929695

### ▼ Statistical Analysis 1

Statistical Analysis Overview	Comparison Group Selection	Grade IIa GVHD; 0.5 mg/kg/d Prednisone, Grade IIa GVHD; 1.0 mg/kg/d Prednisone
	Comments	[Not Specified]
	Type of Statistical Test	Superiority or Other
	Comments	[Not Specified]
Statistical Test of Hypothesis	P-Value	0.08
	Comments	[Not Specified]
	Method	t-test, 2 sided
	Comments	[Not Specified]

### ▼ Statistical Analysis 2

Statistical Analysis Overview	Comparison Group Selection	Grade IIb-IV GVHD; 1.0 mg/kg/d Prednisone, Grade IIb-IV GVHD; 2.0 mg/kg/d Prednisone
	Comments	[Not Specified]
	Type of Statistical Test	Superiority or Other
	Comments	[Not Specified]
Statistical Test of Hypothesis	P-Value	0.4
	Comments	[Not Specified]
	Method	t-test, 2 sided
	Comments	[Not Specified]



An initiative of the ABIM Foundation

American Society for Blood and Marrow Transplantation  
and the Canadian Blood and Marrow Transplant Group



## Five Things Physicians and Patients Should Question

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### **Don't routinely use peripheral blood stem cells for patients with aplastic anemia when a suitable bone marrow donor is available due to a higher risk of graft-versus-host disease.**

While faster engraftment with filgrastim-mobilized peripheral blood stem cells results in quicker recovery of peripheral blood counts compared to bone marrow in patients with aplastic anemia, the higher rate of graft-versus-host disease may be detrimental.

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3

### **Don't routinely use two cord blood units for standard umbilical cord blood transplantation when a single unit of adequate size is available, recognizing that higher cell doses are preferred when using units with greater HLA mismatch.**

Randomized trials demonstrate similar clinical outcomes after single-unit and double-unit umbilical cord blood transplantation, including comparable rates of relapse, engraftment failure, overall survival, and transplantation related mortality. Moreover, graft-versus-host disease may be more frequent after double-cord blood transplantation.

4

### **Don't routinely use peripheral blood stem cells for matched unrelated donor transplantation using myeloablative conditioning and standard graft-versus-host disease prevention regimens when a suitable bone marrow donor is available.**

Patients undergoing myeloablative matched unrelated donor hematopoietic cell transplantation with standard graft-versus-host disease prophylaxis (calcineurin inhibitor and methotrexate) with a peripheral blood stem cell graft experience more symptomatic chronic graft-versus-host disease than those receiving bone marrow, without affecting relapse rates or overall survival. Peripheral blood stem cells may be considered in cases with substantial recipient/donor size discrepancy, donor preference, and for malignant diseases with high risk for graft failure.

5

### **Don't routinely give immunoglobulin replacement to adult hematopoietic cell transplantation recipients in the absence of recurrent infections regardless of the IgG level.**

Meta-analyses of controlled trials conclude that immunoglobulin replacement offers no advantage for infection prevention and overall survival, and may predispose to a higher risk of hepatic sinusoidal obstruction syndrome and venous thromboembolism, and impair the efficacy of post-transplant vaccinations. There may be subsets of patients where prophylactic immunoglobulin replacement may be considered, such as in umbilical cord blood transplant recipients, in children undergoing transplantation for inherited or acquired disorders associated with B-cell deficiency, and in chronic graft-versus-host disease patients with recurrent sino-pulmonary infections.

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- ***Daha yüksek hücre dozlarının yüksek HLA uyumsuzluğu olan ürünlerde tercih edildiğini akılda tutarak, yeterli dozda hücre içeren tek ünite ürün varlığında standart kordon kanı naklinde çift ünite kordon kanı ürününü rutin olarak kullanmayın***
  - Randomize çalışmalar, tek ünite ve çift ünite kordon kanı naklinin karşılaştırılabilir relaps, engraftman yetmezliği, yaşam süresi ve transplant ilişkili mortalite oranları ile birlikte benzer klinik sonuçlara sahip olduklarını göstermiştir. Ek olarak, çift ünite kordon kanı naklinden sonra GVHH daha sık olabilmektedir.

- Uygun HLA-eş akraba veya akrabadışı vericisi olmayan hastalarda kordon kanı KHN alternatif kök hücre kaynağı olarak düşünülmelidir
- Kordon kanı KHN'lerinin, önerilen ulusal hazırlama rejimleri kullanılarak JACIE akredite merkezlerde yapılmasını önermektedir
- Ulusca olarak kabul görmüş verici seçim algoritmasının kullanılması önerilmektedir
- Spesifik kordon kanı ünitesinin seçimi kompleks bir durumdur. Ulusca olarak kabul görmüş kişisel kordon kanı ünitesi seçim kriterleri kullanılmalıdır

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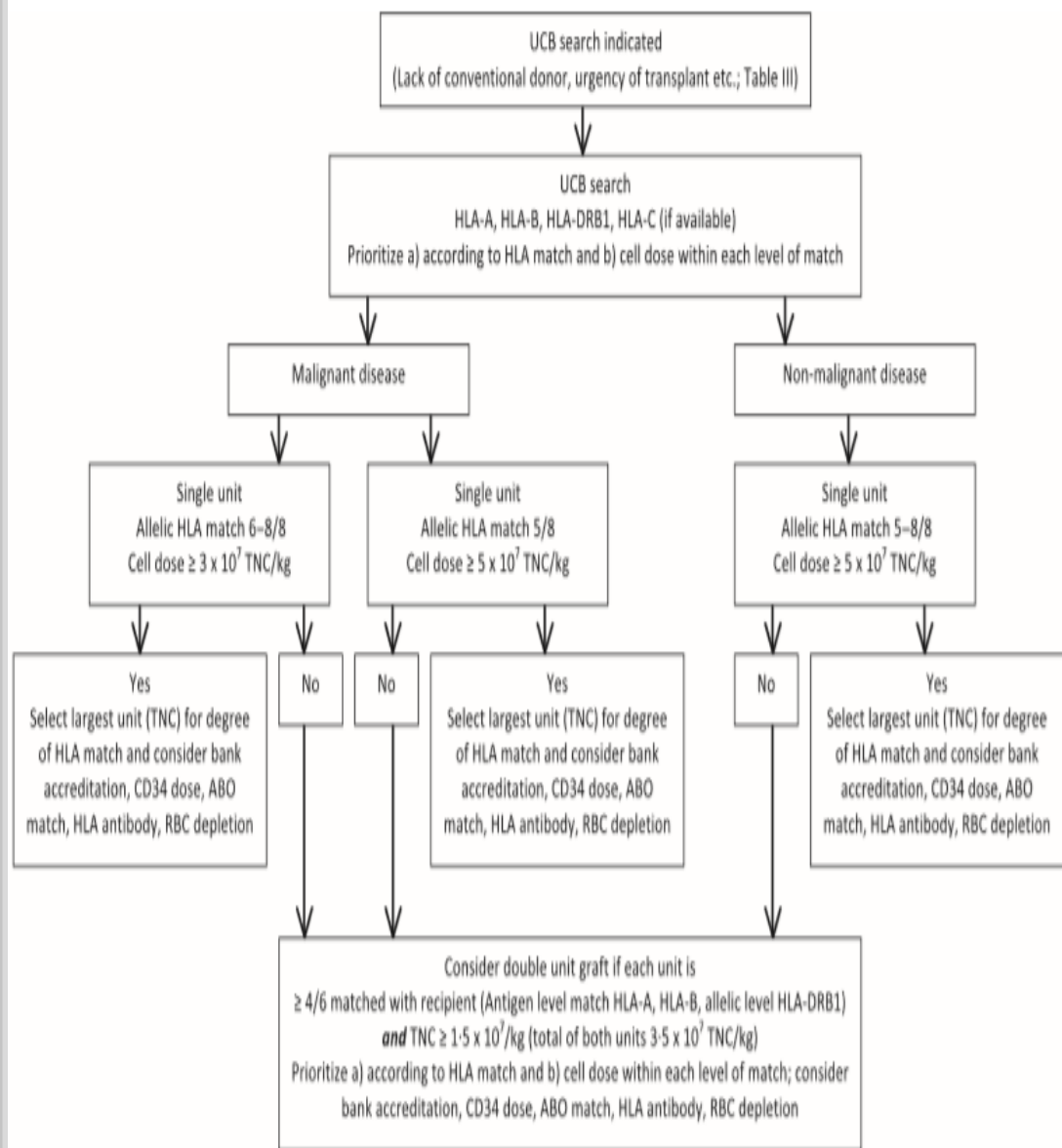
**bjh** guideline

**Recommendations for a standard UK approach to incorporating umbilical cord blood into clinical transplantation practice: an update on cord blood unit selection, donor selection algorithms and conditioning protocols**

Rachael Hough,<sup>1</sup> Robert Danby,<sup>2</sup> Nigel Russell,<sup>3</sup> David Marks,<sup>4</sup> Paul Veys,<sup>5</sup> Bronwen Shaw,<sup>6</sup> Rob Wynn,<sup>7</sup> Ajay Vora,<sup>8</sup> Stephen Mackinnon,<sup>9</sup> Karl S. Peggs,<sup>10</sup> Charles Crawley,<sup>10</sup> Charlie Craddock,<sup>11</sup> Antonio Pagliuca,<sup>12</sup> Gordon Cook,<sup>13</sup> John A. Snowden,<sup>14</sup> Andrew Clark,<sup>15</sup> Judith Marsh,<sup>15</sup> Sergio Querol,<sup>16,17</sup> Guy Parkes,<sup>18</sup> Henny Braund<sup>18</sup> and Vanderson Rocha<sup>19</sup>

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*British Journal of Haematology*, 2016, **172**, 360–370





- Faz III, çok merkezli, randomize çalışma
- 2006 – 2012 yılları, 1-21 yaşları arasında hematolojik kansere sahip 224 hasta
- 1:1 oranda rastgele tek ünite vs çift ünite kordon kanı KHN
- Myeloablatif hazırlama rejimi ve GVHH profilaksi yaklaşımı uniform
- Birincil sonlanım – 1 yıllık yaşam süresi

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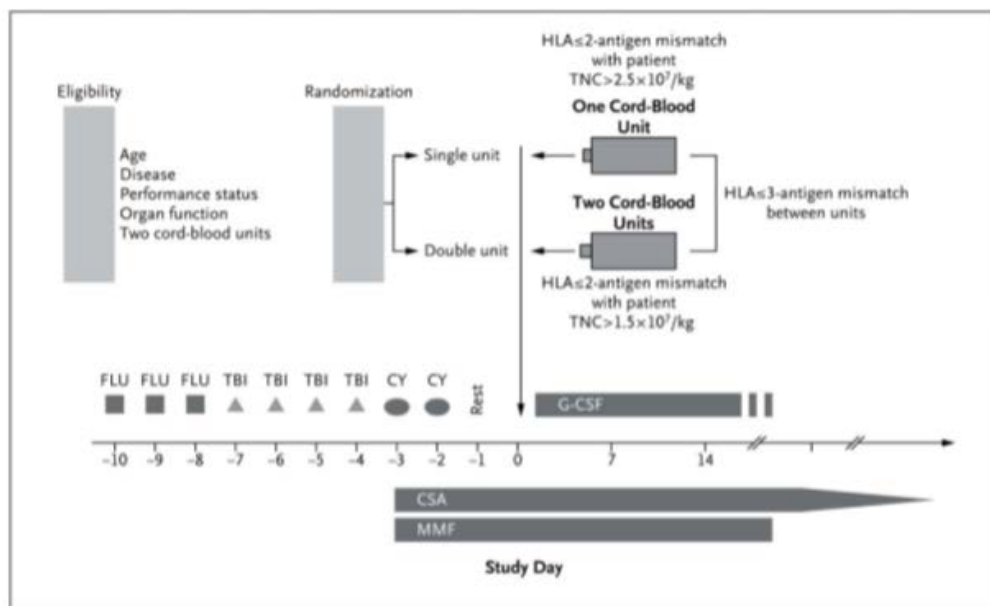
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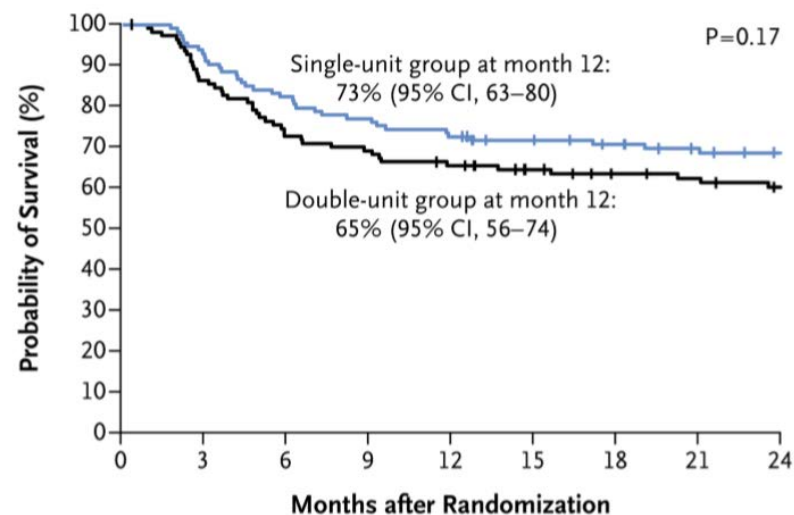
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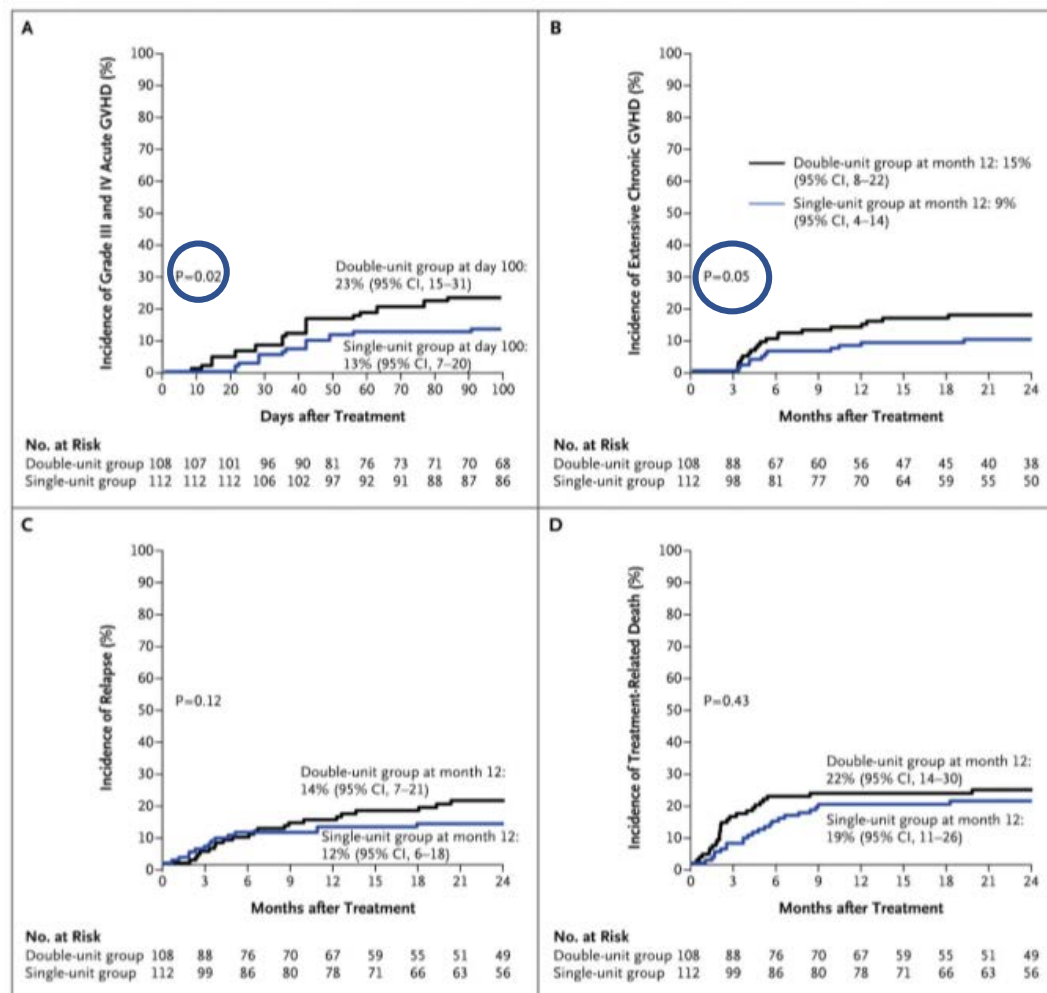
## No. at Risk

Double-unit group	111	95	80	76	71	64	59	57	54
Single-unit group	113	103	93	87	82	75	71	66	63



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- ***Uygun kemik iliği vericisi varlığında, miyeloablatif hazırlama rejimi ve standart GVHH profilaksi rejimleri kullanılan HLA-eş akrabadışı KHN'inde rutin olarak periferik kaynaklı kök hücre kullanmayın***
  - Standart GVHH profilaksisi (kalsinörin inh ve Mtx) eşliğinde periferik kök hücre kullanılarak HLA-eş akrabadışı nakil yapılan hastalar kemik iliği kök hücre kullanılan hastalara oranla relaps ve yaşam süresi etkilenmemekle birlikte daha fazla semptomatik kronik GVHH ile karşı karşıya kalmaktadır.

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- Faz III, çok merkezli, randomize çalışma
- 2004 – 2009 yılları, 48 merkez, < 66 yaş 551 hasta
- 1:1 oranda periferik vs kemik iliği akrabadışı KHN
- Ortanca takip süresi – 3 yıl
- Birincil sonlanım – 2 yıllık yaşam süresi



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Characteristic	Bone Marrow (N = 278)	Peripheral-Blood Stem Cells (N = 273)
Karnofsky performance-status score $\geq 90\%$ — no./total no. (%) <sup>§</sup>	172/240 (72)	154/228 (68)
Seropositivity for cytomegalovirus — no./total no. (%)	142/263 (54)	123/261 (47)
Conditioning regimen — no. (%)		
Cyclophosphamide and total-body irradiation <sup>§</sup>	133 (48)	133 (49)
Cyclophosphamide and busulfan <sup>**</sup>	90 (32)	75 (27)
Fludarabine, busulfan, and antithymocyte globulin <sup>††</sup>	39 (14)	40 (15)
Fludarabine and melphalan <sup>‡‡</sup>	16 (6)	25 (9)
GVHD prophylaxis — no. (%)		
Cyclosporine and methotrexate	67 (24)	59 (22)
Tacrolimus and methotrexate	183 (66)	196 (72)
Other	28 (10)	18 (7)
Did not undergo transplantation — no. (%)	14 (5)	11 (4)
Antithymocyte globulin treatment — no./total no. (%) <sup>§§</sup>	65/258 (25)	72/255 (28)
No. of donor mismatches at <i>HLA-A, B, C</i> , and <i>DRB1</i> — no./total no. (%) <sup>¶¶</sup>		
0	200/264 (76)	209/262 (80)
1	55/264 (21)	50/262 (19)
2	7/264 (3)	3/262 (1)
3	2/264 (1)	0/262
CD34+ cell dose per kilogram ( $\times 10^{-6}$ ) <sup>§§</sup>		
Median	2.75	7.70
Interquartile range	1.94–4.53	5.43–11.28

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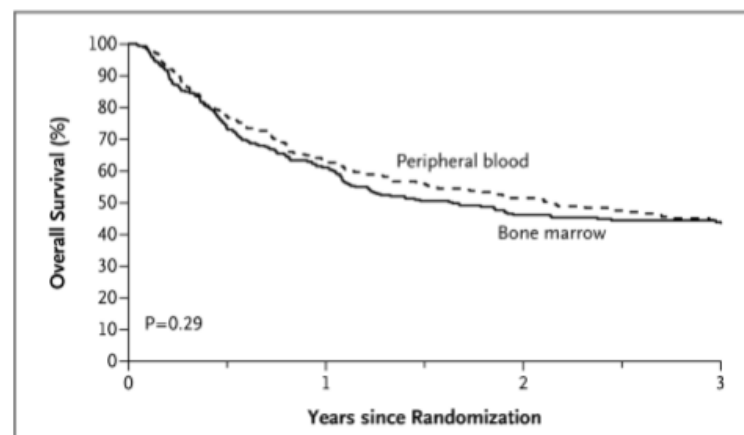
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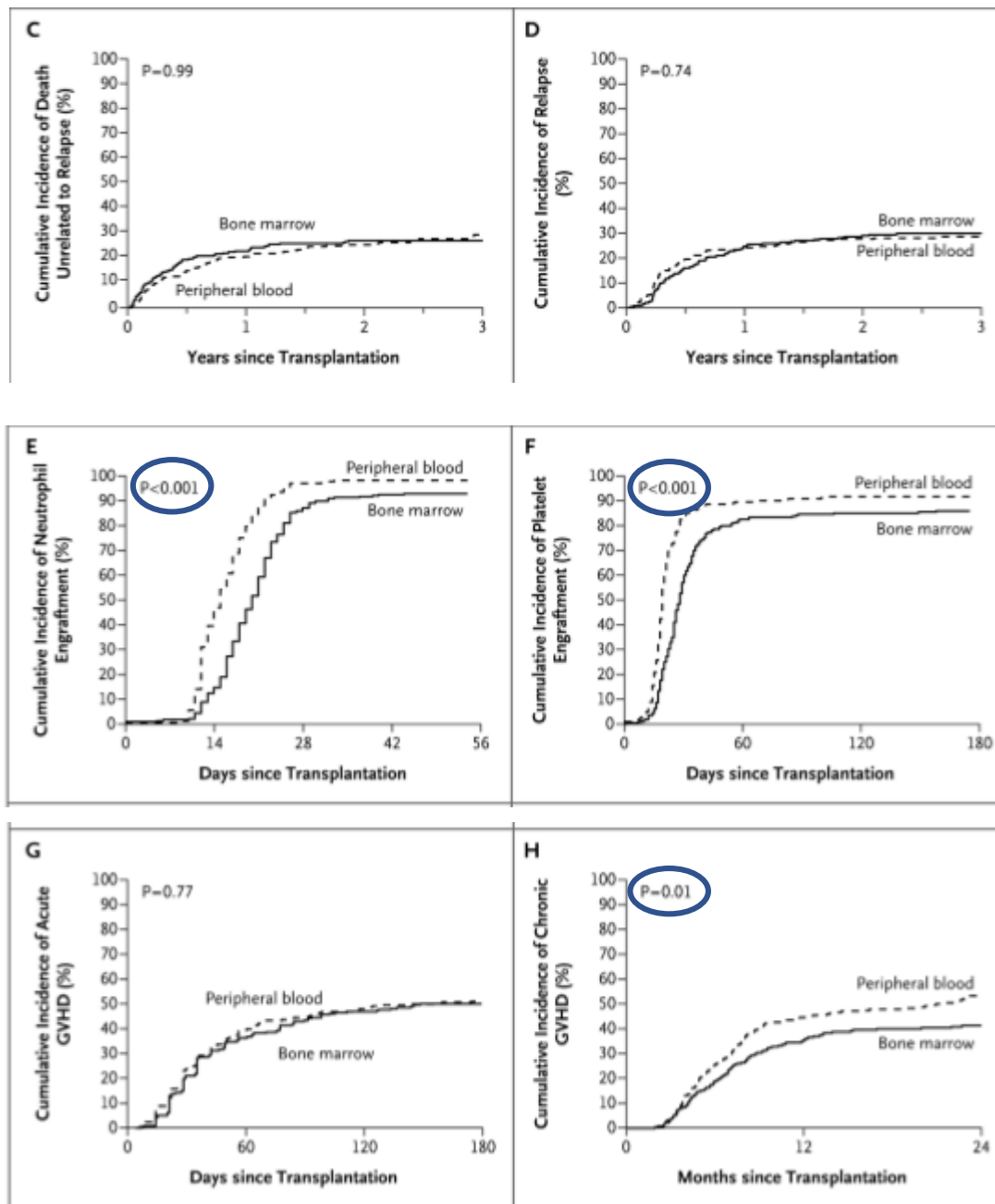
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**Figure 1. Survival after Randomization in the Intention-to-Treat Analysis**

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Claudio Anasetti, M.D., Brent R. Logan, Ph.D., Stephanie J. Lee, M.D., M.P.H., Edmund K. Waller, M.D., Ph.D., Daniel J. Weisdorf, M.D., John R. Wingard, M.D., Corey S. Cutler, M.D., M.P.H., Peter Westervelt, M.D., Ph.D., Ann Woolfrey, M.D., Stephen Couban, M.D., Gerhard Ehninger, M.D., Laura Johnston, M.D., Richard T. Maziarz, M.D., Michael A. Pulsipher, M.D., David L. Porter, M.D., Shin Mineishi, M.D., John M. McCarty, M.D., Shakila P. Khan, M.D., Paolo Anderlini, M.D., William I. Bensinger, M.D., Susan F. Leitman, M.D., Scott D. Rowley, M.D., Christopher Bredeon, M.D., Shelly L. Carter, Sc.D., Mary M. Horowitz, M.D., and Dennis L. Confer, M.D. for the Blood and Marrow Transplant Clinical Trials Network

Don't routinely use peripheral blood stem cells for matched unrelated donor transplantation using myeloablative conditioning and standard graft-versus-host disease prevention regimens when a suitable bone marrow donor is available.

Patients undergoing myeloablative matched unrelated donor hematopoietic cell transplantation with standard graft-versus-host disease prophylaxis (calcineurin inhibitor and methotrexate) with a peripheral blood stem cell graft experience more symptomatic chronic graft-versus-host disease than those receiving bone marrow, without affecting relapse rates or overall survival. Peripheral blood stem cells may be considered in cases with substantial recipient/donor size discrepancy, donor preference, and for malignant diseases with high risk for graft failure.



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**Bone marrow is associated with better patient-reported outcomes than peripheral blood in survivors 5 years after unrelated donor transplantation**

Stephanie J Lee, M.D.<sup>1</sup>, Brent Logan, Ph.D.<sup>2</sup>, Peter Westervelt, M.D.<sup>3</sup>, Corey Cutler, M.D.<sup>4</sup>, Ann Woolfrey, M.D.<sup>5</sup>, Shakila P. Khan, M.D.<sup>6</sup>, Edmund K. Waller, M.D.<sup>7</sup>, Richard T. Maziarz, M.D.<sup>8</sup>, Juan Wu, M.S.<sup>9</sup>, Bronwen Shaw, M.D.<sup>10</sup>, Dennis Confer, M.D.<sup>11</sup>, Mary M. Horowitz, M.D.<sup>10</sup>, and Claudio Anasetti, M.D.<sup>12</sup>

- Faz III, çok merkezli, randomize çalışma
- 2004 – 2009 yılları, 16 - 66 yaş
- 5. yıl sonunda yaşayan ve değerlendirmeye alınan 102 kemik iliği ve 93 periferik kan akra badışı KHN



**Don't routinely use peripheral blood stem cells for matched unrelated donor transplantation using myeloablative conditioning and standard graft-versus-host disease prevention regimens when a suitable bone marrow donor is available.**

Patients undergoing myeloablative matched unrelated donor hematopoietic cell transplantation with standard graft versus host disease prophylaxis (tacrolimus inhibitor and methotrexate) with a peripheral blood stem cell graft experience more symptomatic chronic graft-versus-host disease than those receiving bone marrow, without affecting relapse rates or overall survival. Peripheral blood stem cells may be considered in cases with substantial recipient/donor size discrepancy, donor preference, and for malignant diseases with high risk for graft failure.



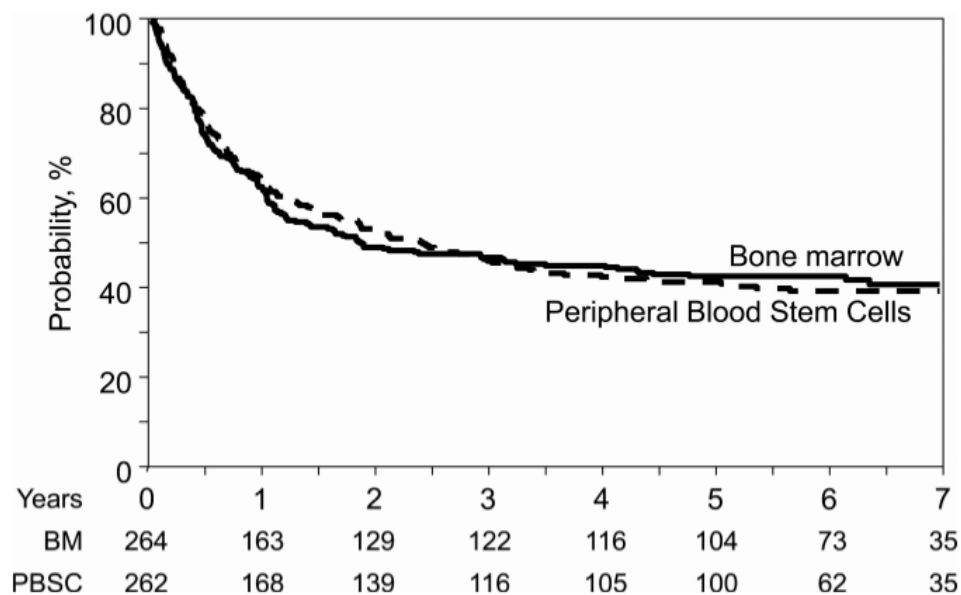
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**Figure 1.**  
Overall Survival

# Don't routinely use peripheral blood stem cells for matched unrelated donor transplantation using myeloablative conditioning and standard graft-versus-host disease prevention regimens when a suitable bone marrow donor is available.

Patients undergoing myeloablative matched unrelated donor hematopoietic cell transplantation with standard graft-versus-host disease prophylaxis (calcineurin inhibitor and methotrexate) with a peripheral blood stem cell graft experience more symptomatic chronic graft-versus-host disease than those receiving bone marrow, without affecting relapse rates or overall survival. Peripheral blood stem cells may be considered in cases with substantial recipient/donor size discrepancy, donor preference, and for malignant diseases with high risk for graft failure.



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Comparison of primary patient-reported values at five years between bone marrow and peripheral blood recipients at five years, adjusted for enrollment values and missing data using inverse probability weighting using significant clinical characteristics.

Patient-reported measure	Adjusted for enrollment values and missing data using inverse probability weighting using significant clinical characteristics				Clinically significant difference *	Adjusted for missing data using multiple imputation		
	Bone marrow (n=102)	Peripheral blood (n=93)	P value	Difference between bone marrow and peripheral blood (95% CI)		Difference between bone marrow and peripheral blood (95% CI) under MAR assumption	P value	Tipping Point
<b>FACT-BMT TOI (higher scores better)</b>			0.014	6.2 (1.3-11.1)	8.5	6.4 (1.4-11.3)	0.012	0.3
Mean +/- SE	76.7 +/- 1.6 (n=79)	70.5 +/- 1.9 (n=69)						
<b>MHI - Psychological well-being (higher scores better)</b>			0.011	6.7 (1.6-11.8)	8.4	7.4 (2.5-12.2)	0.003	-5.1
Mean +/- SE	78.9 +/- 1.7 (n=80)	72.2 +/- 1.9 (n=72)						
<b>MHI - Psychological Distress (lower scores better)</b>			0.128	-3.0 (-6.8,0.9)	6.5	-4.1 (-8.1,0.2)	0.039	-3.9
Mean +/- SE	16.0 +/- 1.3 (n=80)	19.0 +/- 1.5 (n=71)						
<b>Chronic GVHD symptoms (lower scores better)</b>			0.004	-6.3 (-10.5, -2.0)	7.1	-8.4 (-12.7, -4.1)	<0.001	12.6
Mean +/- SE	13.1 +/- 1.5 (n=80)	19.3 +/- 1.6 (n=72)						

FACT-BMT TOI, Functional assessment of cancer therapy; bone marrow transplant subscale, Trial Outcome Index; MHI, Mental health inventory; GVHD, graft-versus-host disease; SE, standard error; MAR=Missing at Random; Tipping Point=shifted difference in mean outcome between BM and PB for missing values which would lead to a different conclusion at alpha=0.0125

\* clinically significant difference = 0.5 × standard deviation



An initiative of the ABIM Foundation

American Society for Blood and Marrow Transplantation  
and the Canadian Blood and Marrow Transplant Group



## Five Things Physicians and Patients Should Question

1

### **Don't routinely use peripheral blood stem cells for patients with aplastic anemia when a suitable bone marrow donor is available due to a higher risk of graft-versus-host disease.**

While faster engraftment with filgrastim-mobilized peripheral blood stem cells results in quicker recovery of peripheral blood counts compared to bone marrow in patients with aplastic anemia, the higher rate of graft-versus-host disease may be detrimental.

2

### **Don't use greater than 2 mg/kg/day of methylprednisolone (or equivalent) for the initial treatment of graft-versus-host disease.**

Published studies have shown no advantage to using methylprednisolone-equivalent doses higher than 2 mg/kg/day in acute graft-versus-host disease. In addition, using higher doses increases risks of corticosteroid related toxicity. Furthermore, at least in patients with grade I-II acute graft-versus-host disease, initial therapy with lower-dose corticosteroids at 1 mg/kg/day may be equivalent.

3

### **Don't routinely use two cord blood units for standard umbilical cord blood transplantation when a single unit of adequate size is available, recognizing that higher cell doses are preferred when using units with greater HLA mismatch.**

Randomized trials demonstrate similar clinical outcomes after single-unit and double-unit umbilical cord blood transplantation, including comparable rates of relapse, engraftment failure, overall survival, and transplantation related mortality. Moreover, graft-versus-host disease may be more frequent after double-cord blood transplantation.

4

### **Don't routinely use peripheral blood stem cells for matched unrelated donor transplantation using myeloablative conditioning and standard graft-versus-host disease prevention regimens when a suitable bone marrow donor is available.**

Patients undergoing myeloablative matched unrelated donor hematopoietic cell transplantation with standard graft-versus-host disease prophylaxis (calcineurin inhibitor and methotrexate) with a peripheral blood stem cell graft experience more symptomatic chronic graft-versus-host disease than those receiving bone marrow, without affecting relapse rates or overall survival. Peripheral blood stem cells may be considered in cases with substantial recipient/donor size discrepancy, donor preference, and for malignant diseases with high risk for graft failure.

5

### **Don't routinely give immunoglobulin replacement to adult hematopoietic cell transplantation recipients in the absence of recurrent infections regardless of the IgG level.**

Meta-analyses of controlled trials conclude that immunoglobulin replacement offers no advantage for infection prevention and overall survival, and may predispose to a higher risk of hepatic sinusoidal obstruction syndrome and venous thromboembolism, and impair the efficacy of post-transplant vaccinations. There may be subsets of patients where prophylactic immunoglobulin replacement may be considered, such as in umbilical cord blood transplant recipients, in children undergoing transplantation for inherited or acquired disorders associated with B-cell deficiency, and in chronic graft-versus-host disease patients with recurrent sino-pulmonary infections.

- ***Erişkin kök hücre nakli alıcılarına, Ig G düzeyi kaç olursa olsun tekrarlayan enfeksiyonlar olmadıkça rutin immünglobulin replasmanı yapılmamalıdır***
- Kontrollü çalışmaların metaanalizleri, immünglobulin replasmanının yaşam süresi ve enfeksiyon önleminde herhangi bir avantaj sunmadığı gibi venöz tromboemboli ve hepatik sinusoidal tıkanma sendromu riskini arttırabileceğini ve nakil sonrası aşılamanın etkinliğini azaltabileceğini göstermiştir. Kordon kanı nakilleri, B-hücre eksikliği nedeniyle nakil olacak çocuklar ve tekrarlayan sino-pulmoner enfeksiyonları olan kronik GVHH sahip hastalar gibi bir grup hastada proflaktik immünglobulin replasmanı düşünülebilir.

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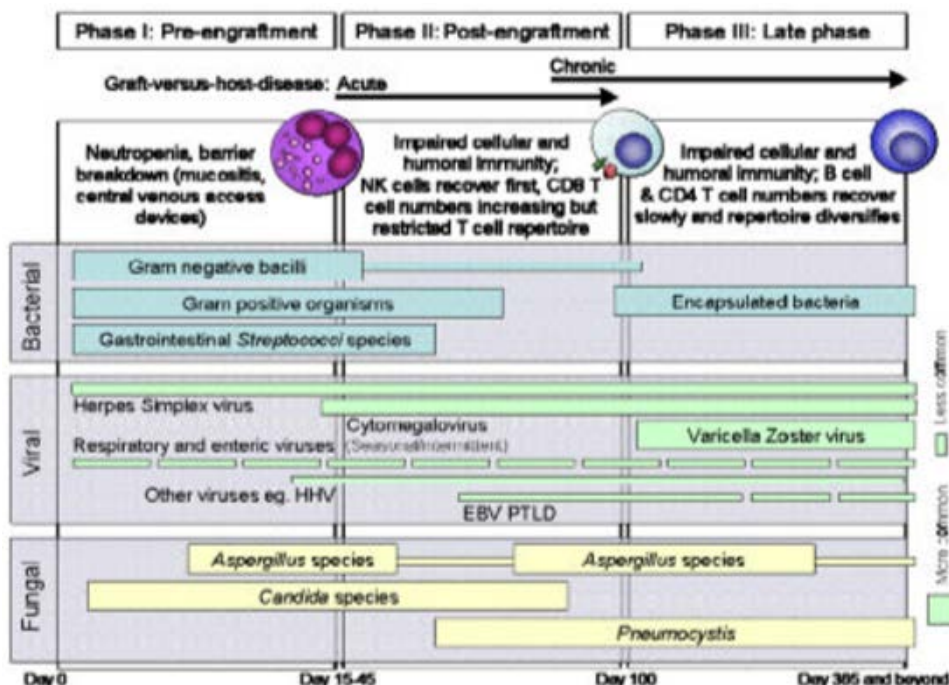
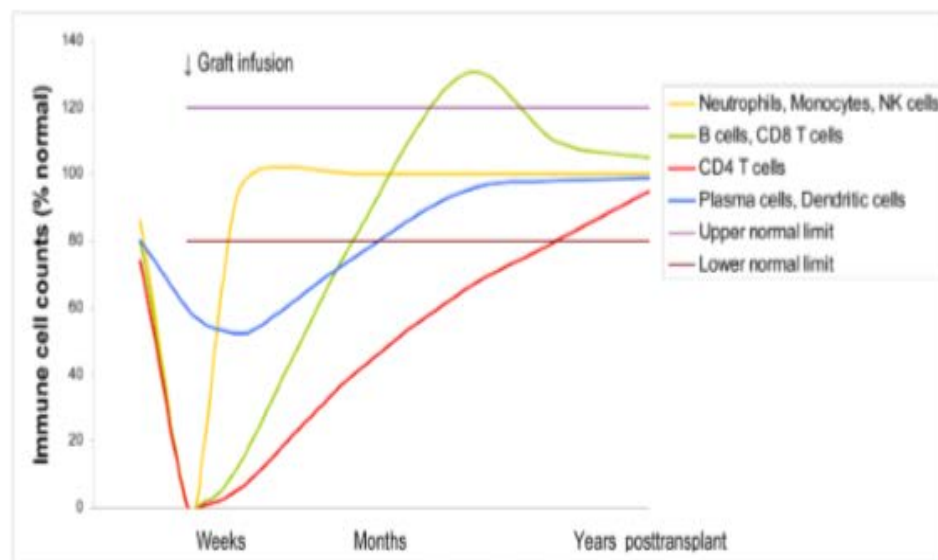
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## Guidelines for Preventing Infectious Complications among Hematopoietic Cell Transplant Recipients: A Global Perspective

Recommendations of the Center for International Blood and Marrow Transplant Research (CIBMTR®), the National Marrow Donor Program (NMDP), the European Blood and Marrow Transplant Group (EBMT), the American Society of Blood and Marrow Transplantation (ASBMT), the Canadian Blood and Marrow Transplant Group (CBMTG), the Infectious Disease Society of America (IDSA), the Society for Healthcare Epidemiology of America (SHEA), the Association of Medical Microbiology and Infectious Diseases Canada (AMMI), and the Centers for Disease Control and Prevention (CDC), Marcie Tomblyn, Tom Chiller, Hermann Einsele, Ronald Gress, Kent Sepkowitz, Jan Storek, John R Wingard, Jo-Anne H Young, and Michael A Boeckh





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## Pathogen: Bacterial infections during the first 100 days after HCT

Indication	First Choice	Alternatives
Prevention of bacterial infections for <i>adult</i> HCT patients with anticipated neutropenic periods of 7 days or more	A fluoroquinolone with antipseudomonal activity (ie, levofloxacin 500 mg once daily (BI) or ciprofloxacin 500 mg twice daily (BII)) <ul style="list-style-type: none"> <li>Start at the time of stem cell infusion and continue until recovery from neutropenia or initiation of empirical antibacterial therapy for febrile neutropenia;</li> <li>Local epidemiological data regarding fluoroquinolone resistance patterns should be carefully considered before applying its prophylaxis (AIII). Closely monitor for emergence of fluoroquinolone resistance (AIII)</li> </ul>	Azithromycin 250 mg once daily (CIII)
Prevention of bacterial infections among <i>adult</i> or <i>adolescent</i> HCT recipients with severe hypogammaglobulinemia (ie, serum IgG level <400 mg/dL)	IVIG, 500 mg/kg/week (CIII)*†	None
Prevention of bacterial infections among allogeneic <i>pediatric</i> HCT recipients with severe hypogammaglobulinemia (ie, serum IgG level <400 mg/dL)	IVIG, 400 mg/kg/month (CIII)*†	None

## Pathogen: Bacterial infections beyond 100 days post-HCT

Indication	First Choice
Prevention of late bacterial infections with antibiotic prophylaxis	Prolonged antibiotic prophylaxis is recommended only for preventing infection with <i>S. pneumoniae</i> among allogeneic recipients with cGVHD (see below).
Prevention of late bacterial infections with vaccinations	Immunizations (Table 6) are recommended for preventing infection with <i>S. pneumoniae</i> and <i>H. influenzae</i> type b.
Prevention of bacterial infections among HCT recipients with severe	IVIG, 500 g/kg every 3–4 weeks (CIII)

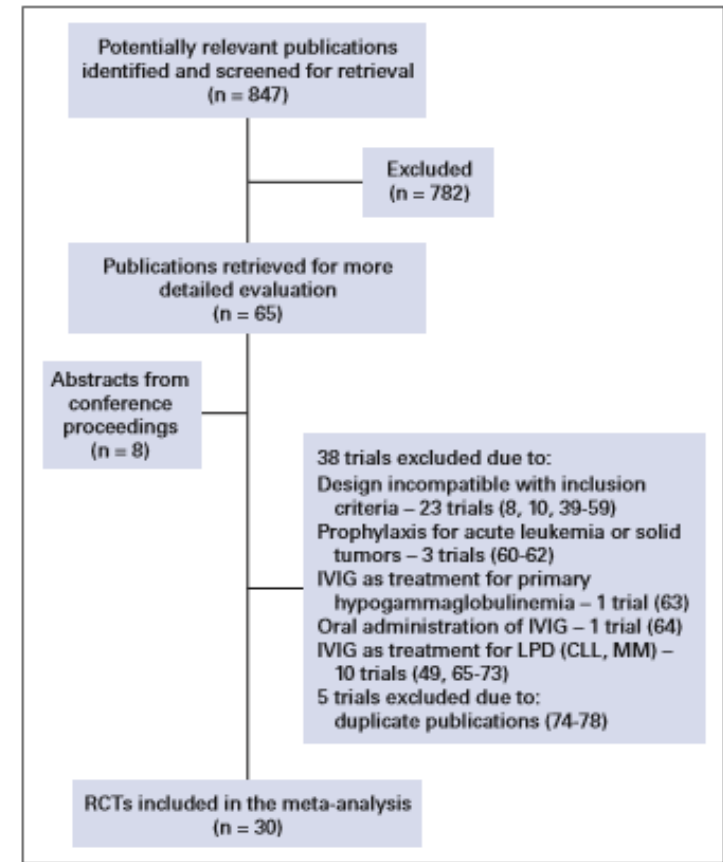
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## Immunoglobulin Prophylaxis in Hematopoietic Stem Cell Transplantation: Systematic Review and Meta-Analysis

*Pia Raanani, Anat Gafner-Gvili, Mical Paul, Isaac Ben-Bassat, Leonard Leibovici, and Ofer Shpilberg*

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Meta-analyses of controlled trials conclude that immunoglobulin replacement offers no advantage for infection prevention and overall survival, and may predispose to a higher risk of hepatic sinusoidal obstruction syndrome and venous thromboembolism, and impair the efficacy of post-transplant vaccinations. There may be subsets of patients where prophylactic immunoglobulin replacement may be considered, such as in umbilical cord blood transplant recipients, in children undergoing transplantation for inherited or acquired disorders associated with B-cell deficiency, and in chronic graft-versus-host disease patients with recurrent sino-pulmonary infections.



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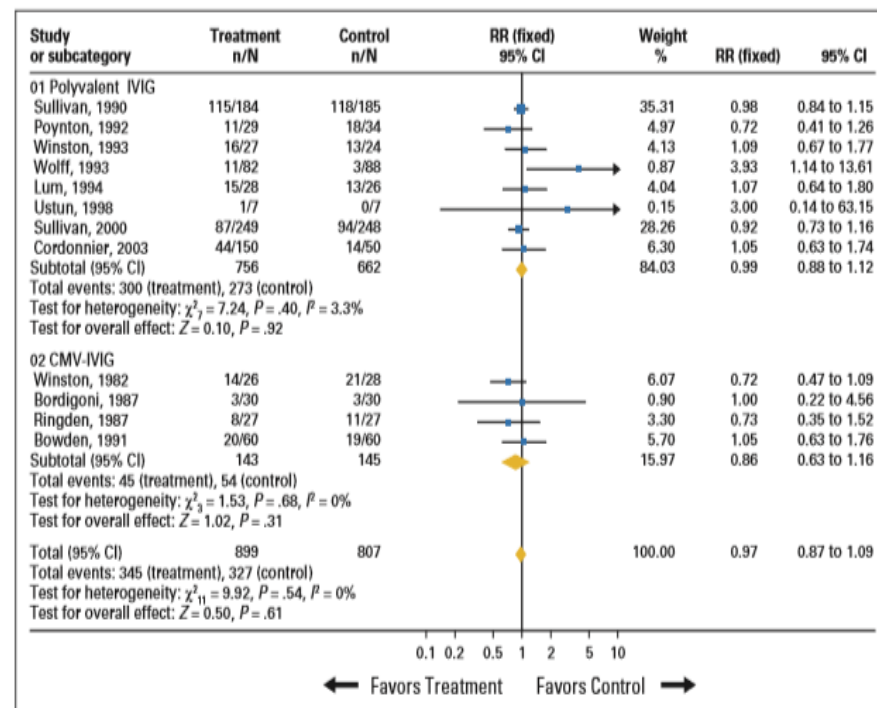
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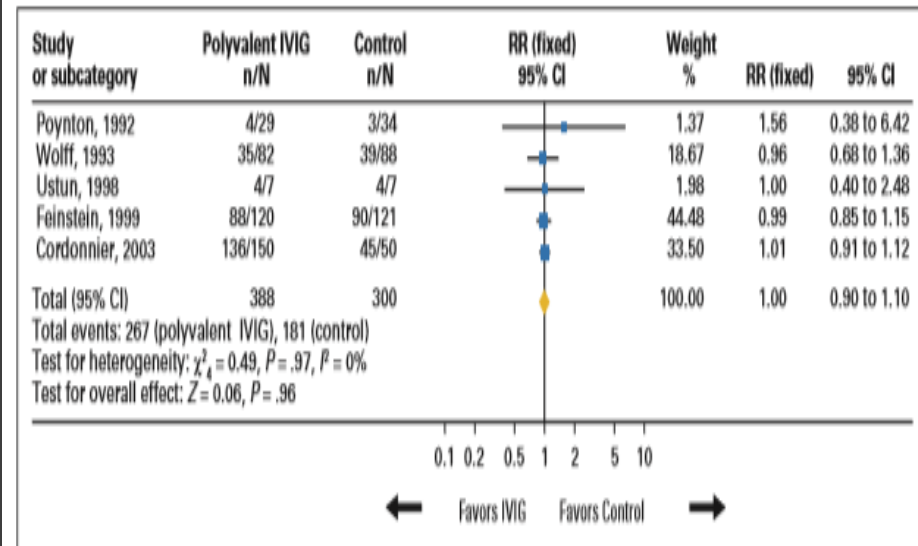
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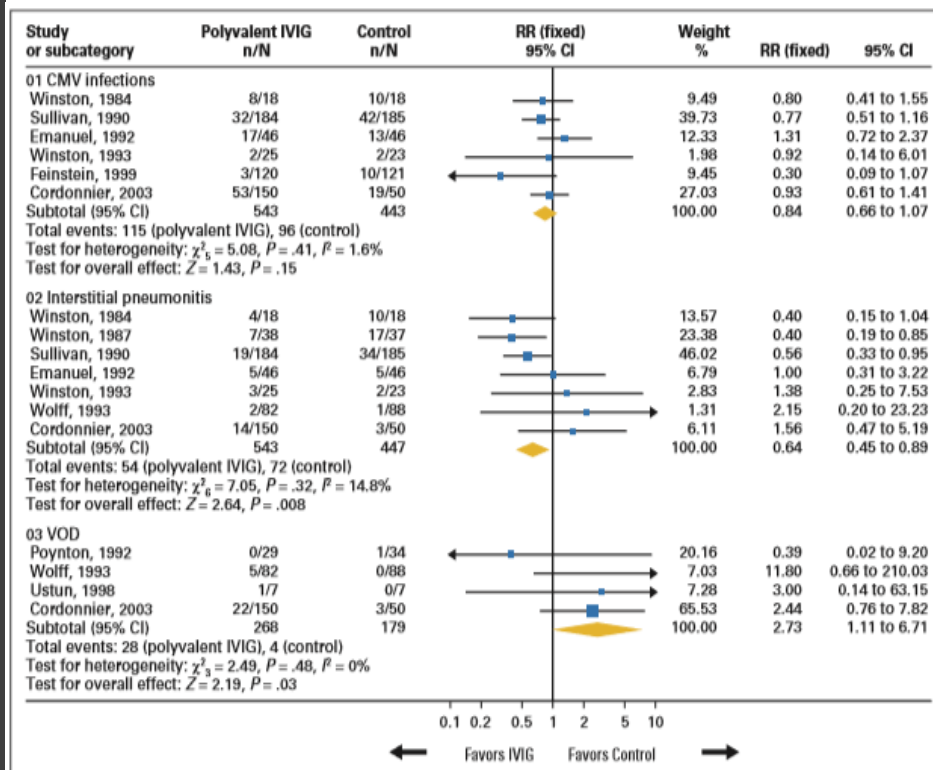
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**Table 2.** Comparison Between Various Meta-Analyses of Prophylaxis IVIG in BMT Patients

Study	No. of Studies	Type of Participants	Clinical Outcome			
			All Cause Mortality	CMV Infection	Interstitial Pneumonia	Acute GVHD
Bass et al <sup>13</sup>	12	BMT recipients	Significantly reduced by IVIG	Not significantly reduced by IVIG	Significantly reduced by IVIG	Not significantly reduced by IVIG
Glowacki et al <sup>14</sup>	18	BMT recipients and solid organ recipients	Not significantly reduced by IVIG	Significantly reduced by IVIG	NA	NA
Raanani et al (this study)	30	BMT	Not significantly reduced by IVIG	Not significantly reduced by IVIG	Significantly reduced by IVIG	Not significantly reduced by IVIG

Abbreviations: BMT, bone marrow transplantation; CMV, cytomegalovirus; GVHD, graft-versus-host disease; IVIG, immunoglobulin; NA, not available.

In conclusion, lack of effect on mortality and lack of difference between the different preparations and doses of polyvalent IVIG do not support a true biologic effect of immunoglobulins in the context of BMT. These agents are associated with adverse effects, a higher rate of VOD, and are costly. Current evidence does not support their use as routine prophylaxis for patients undergoing BMT or HSCT.



SABRINIZ İÇİN TEŞEKKÜR EDERİM

