



## SAA 101: An Introductory Course to Severe Aplastic Anemia

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## Objectives

- Review the diagnostic evaluation done for a patient presenting with low blood counts.
- Review the data regarding treatment options.
- Answers to common questions.

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## What is Aplastic Anemia

- Acquired Aplastic Anemia is a disease caused by too few hematopoietic progenitor cells leading to too few red blood cells, white blood cells, and platelets.
- Acquired Aplastic Anemia needs to be differentiated from an inherited bone marrow failure syndrome.

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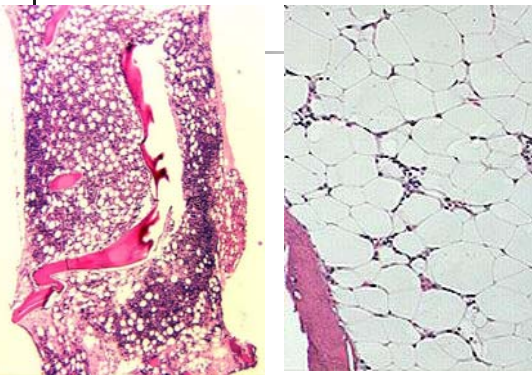
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HEALTHY BONE MARROW    APLASTIC BONE MARROW



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### CRITERIA for SEVERITY of APLASTIC ANEMIA

- SEVERE AA (SAA)
  - PERIPHERAL BLOOD (2 of 3):
    - PMN < 500/ul
    - PLATELETS < 20,000/ul
    - RETICULOCYTES < 20,000/ul (< 1%)
  - MARROW: hypocellular
- VERY SEVERE AA (VSAA): PMN < 200
- MILD AA: LESS AFFECTED THAN SAA

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### When Should I think of Aplastic Anemia?

- Presenting symptoms are most often the same signs as any bone marrow disorder.
- Bruising and Petechiae
  - Differential Dx: ITP/malignancy
- Fatigue/Pallor
  - Differential Dx: AIHA/ Infection/malignancy
- Recurrent Fevers
  - Acquired Neutropenia/malignancy

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## When Should I think of Aplastic Anemia?

- Diagnostic Procedures:
  - CBC with manual differential/retic count
  - Bone Marrow Aspirate and Biopsy
  - Chromosomes/Flow Cytometry to look for malignancy/CD59 expression to look for evidence of paroxysmal nocturnal hemoglobinuria

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## The Bone Marrow is Aplastic: Is it Acquired Aplastic Anemia?

- Important to discriminate between an inherited bone marrow failure syndrome and acquired aplastic anemia.
- Proper treatment is based on the correct diagnosis.
- [www.marrowsfailure.cancer.gov](http://www.marrowsfailure.cancer.gov)

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## Not all aplasia is SAA: Inherited Bone Marrow Failure Syndromes

- "Not just for pediatric presentations"
  - Fanconi Anemia
  - Dyskeratosis Congenita
  - Schwachman-Diamond Syndrome

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## My patient has acquired SAA: What was the trigger?

- Inciting event leads to an immune mediated destruction of blood progenitor cells
  - Young et al. Blood, 15 October 2006, Vol. 108, No. 8, pp. 2509-2519
- Trigger is usually not identified
- Check for CMV, EBV, HHV-6, Parvovirus, Hepatitis viruses
- History of jaundice
- Medication history
- Exposures

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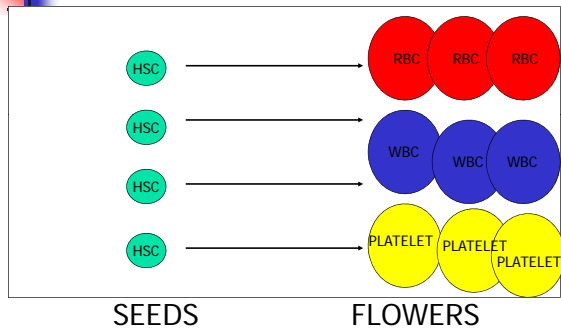
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## The Bone Marrow Garden- Healthy




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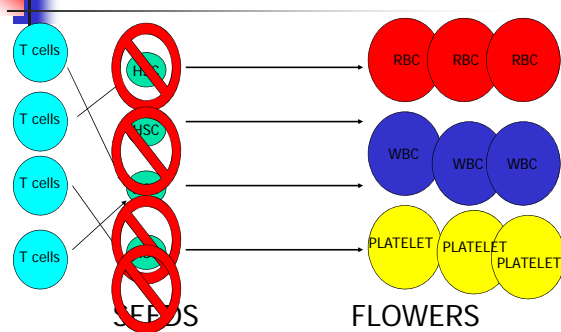
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## The Bone Marrow Garden- Under Attack




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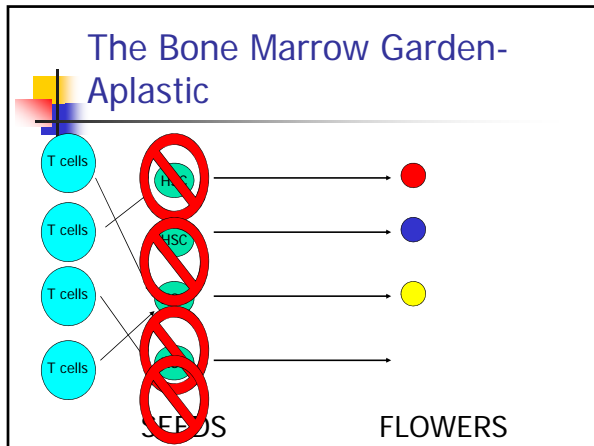
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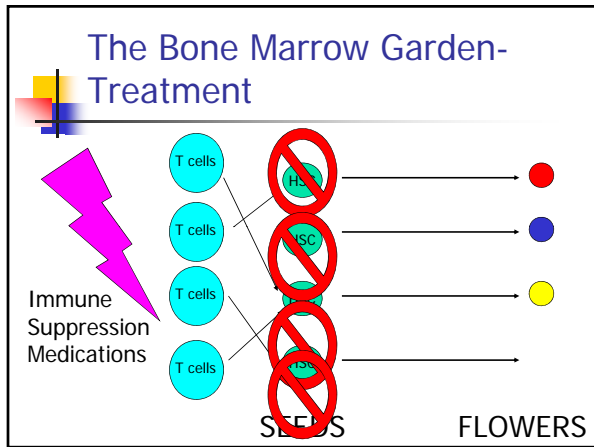
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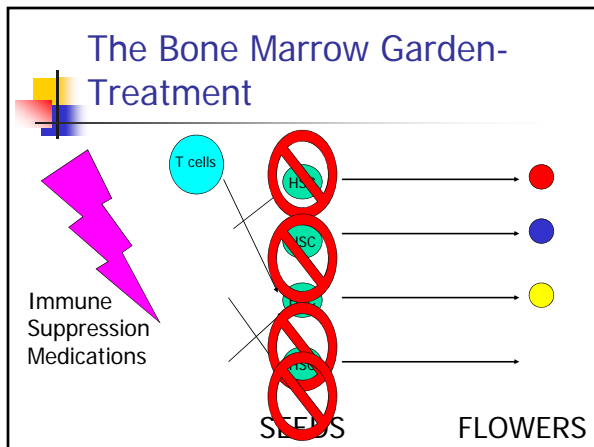
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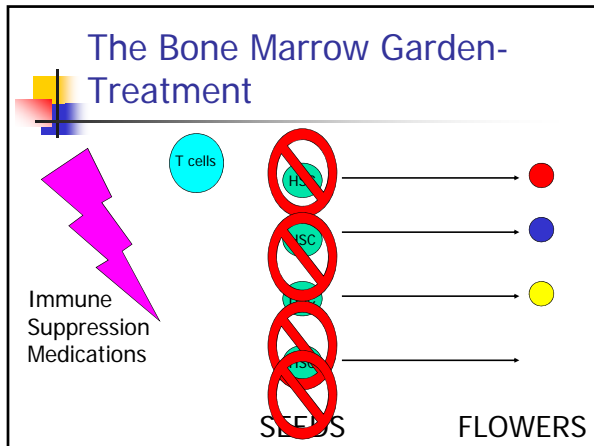
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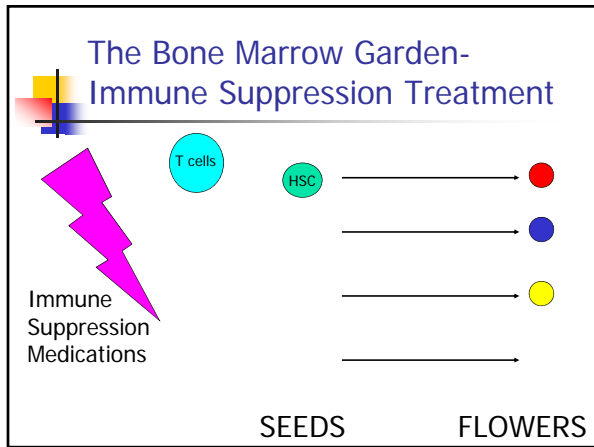
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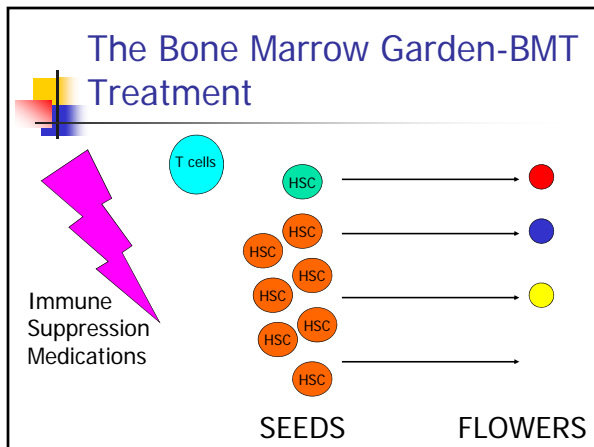
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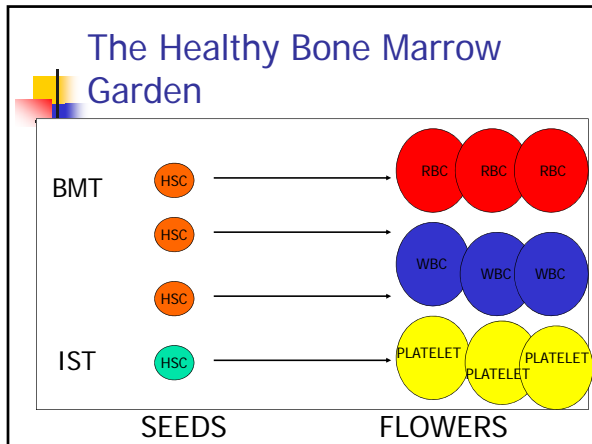
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### Case 1

- 15 year old male with newly diagnosed SAA
- No prior transfusions.
- One sibling has run away from the family and is not in contact.
- Alternatives: Search for the sibling or start an alternative treatment
- Police recommended contacting the media.

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### Conventional Transplant

- HLA matched sibling transplants are an established curative approach to SAA.
- Outcomes to consider are survival, acute GVHD, chronic GVHD, rejection.
- Long-term outcomes to consider include survival, chronic GVHD, late cancers, and fertility.

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## The Seattle Experience-CY/ATG

Kahl et al. British Journal of Haematology 2005

- 1988-2004
- N=81
- Median age=25 years (2-63y)
- Median Duration of SAA=2 months (two weeks-12 years)
- Cyclophosphamide 200 mg/kg and ATG (equine) 90 mg/kg
- MTX/CSA GVHD prevention

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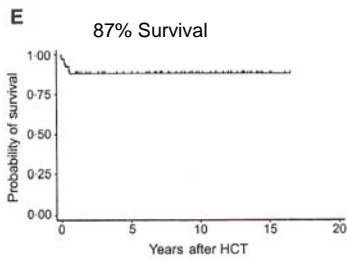
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## Discussion Point-Survival

Kahl et al. British Journal of Haematology 2005



- 78% had performance scores of 100%
- 13% had 90%, 9% < 80
- Seven (all with cGVHD) had avascular joint necrosis.
- 17 successful pregnancies
  - (9 females and 7 partners of male patients)

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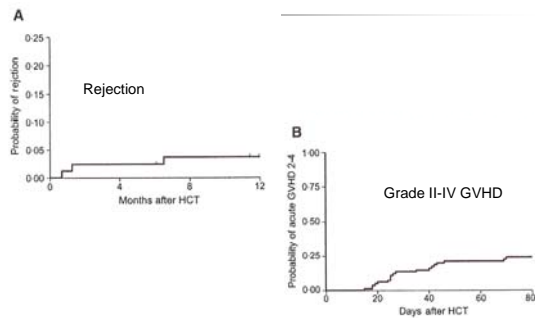
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## The Seattle Experience-CY/ATG

Kahl et al. British Journal of Haematology 2005



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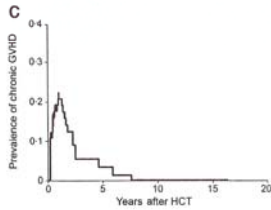
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### Discussion Point-cGVHD

Kahl et al. British Journal of Haematology 2005



- Risk factors for cGVHD:
  - Age >38 years
  - Higher total nucleated marrow cell dose.

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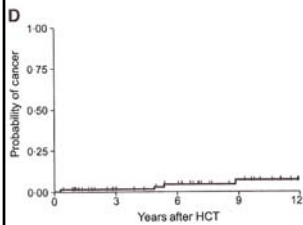
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### Discussion Point-Late Cancers

Kahl et al. British Journal of Haematology 2005



- 6 patients developed cancer.
- 1 PTLD associated with GVHD.
- 1 colon cancer, 3 skin cancers, one mouth cancer (all alive and cancer free)
- Higher cancer rate in those with cGVHD.

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### Take Home Message

- Matched sibling BMT is the treatment of choice for SAA in children and young adults due to the excellent long term survival with very few late effects.

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## Case 2

- 3 year old girl with newly diagnosed SAA
- 3 siblings, no HLA match
- Plan to use Immune Suppression Treatment

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## Immune Suppression Therapy

- Multiple approaches.
- NHLBI and EBMT set the benchmarks.
- NHLBI "gold standard" is ATG/CSA/Prednisone.
- <http://patientrecruitment.nhlbi.nih.gov/AplasticAnemia.aspx>
- Hopkins use of cyclophosphamide.

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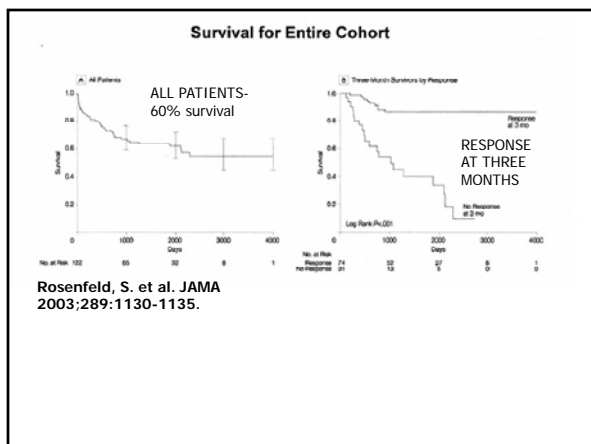
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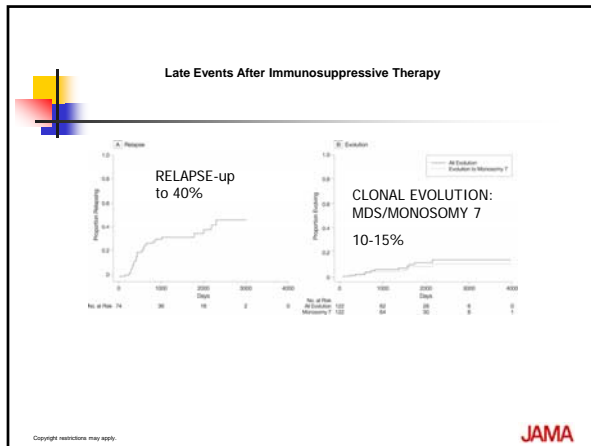
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- ### Take Home Message
- Intensive Immune Suppression Therapy with ATG/CSA/Prednisone remains the treatment of choice for those without a matched sibling.
  - Response at 3 months is crucial for future decisions.
  - Relapse/Clonal evolution are issues.

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- ### Case 3
- 13 year old female with SAA
  - 2 siblings, no HLA match
  - Immune Suppression Treatment-No Response
  - Second Course of Immune Suppression-Still Transfusion Dependent
  - ?Alternative Donor BMT

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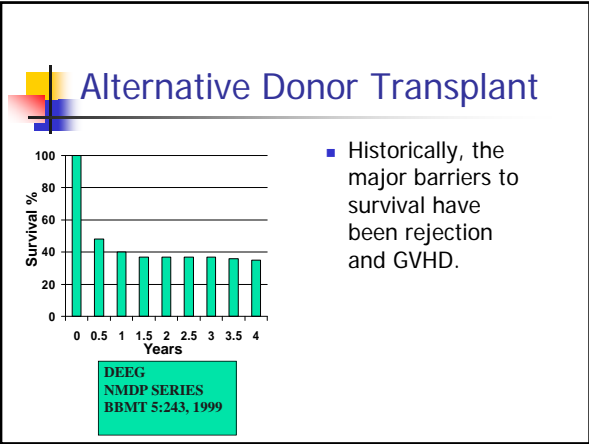
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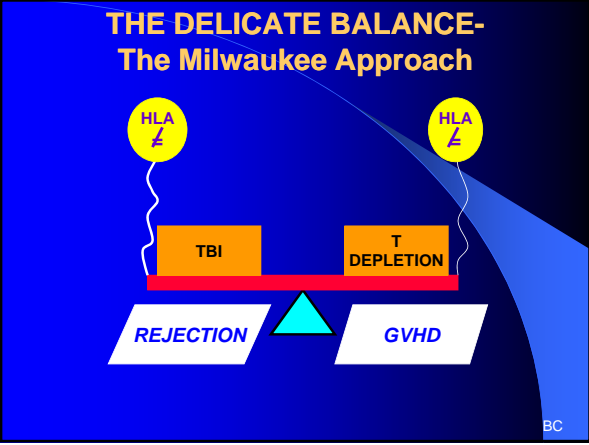
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### Survivorship

- Lance Armstrong Foundation (LAF) defines cancer survivorship as living “with”, “through” and “beyond” cancer (SAA).

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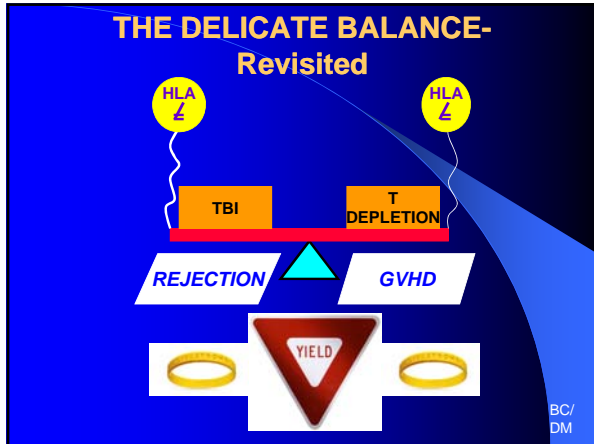
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### What have we learned from historical alternative donor data?

- We need an alternative donor transplant regimen that:
  - Prevents rejection
  - Prevents GVHD
  - Prevents late effects
  - Has excellent long term survival
  - ☺☺☺☺☺☺☺☺
- Deeg et al. and Bacigalupo et al. have published multicenter data with the above goals in mind.

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### The “De-escalating TBI” Experience Deeg et al. BBMT 2001

- 1994-1999; 14 centers
- N=50
- Median age=14 years (1-46y)
- Median Duration of SAA=14 months (3 months-264 months)
- Cyclophosphamide 200 mg/kg and ATG (equine) 90 mg/kg with de-escalation of TBI (3x200cGy; 2x200; 1x200)
- MTX/CSA GVHD prevention

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### The "De-escalating TBI" Experience Deeg et al. BBMT 2001

- Survival was 58% at two years.
- Shorter disease duration and younger age improved survival.
- Unexpectedly high rate of diffuse alveolar damage.
- Data is the basis for current North American CTN trial:
  - Cyclophosphamide de-escalation trial.
  - Fludarabine/ATG/TBI 200 and de-escalating cyclophosphamide starting at 150 mg/kg total CY

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### The EBMT Experience Bacigalupo et al. BMT 2005

- 1998-2004, 13 centers
- N=38
- Median age=14 years (3-37y)
- Median Duration of SAA=20 months (6 weeks-10 years)
- Fludarabine 30 mg/m<sup>2</sup> x 3; CY 10 mg/kg x 4; Thymoglobulin 3.75 mg/kg x 4
- Low dose MTX/CSA GVHD prevention

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### The EBMT Experience Bacigalupo et al. BMT 2005

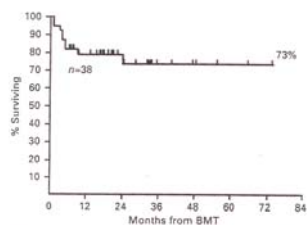


Figure 1 Actuarial survival of 38 patients with acquired SAA undergoing alternative donor transplants.

- Overall survival is 73%
- 7 cases of graft rejection or graft failure (5 alive)
- aGVHD II-III in 11%
- cGVHD in 27%
- Deaths were due to graft failure, EBV-PTLD, hemorrhage.

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The EBMT Experience  
Bacigalupo et al. BMT 2005

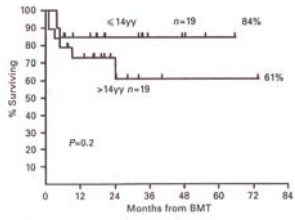


Figure 2 Actuarial survival of patients stratified according to age: there is a trend for improved outcome in patients aged <14 years (84%) as compared to patients aged >14 years (61%).

- Excellent survival without any TBI in the younger cohort.
- EBMT current trial uses a similar regimen with 200 cGy TBI to try to promote engraftment for those over the age of 14 years.

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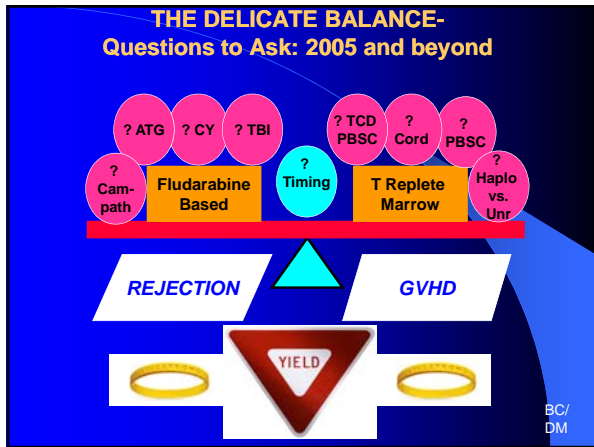
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Take Home Message

- Alternative donor transplant is a feasible option for many patients with SAA.
- Exciting area with improving outcomes with less toxic regimens.
- Timing?!!

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## Conclusions: BMT for SAA

- CY/ATG provides excellent results for patients with an HLA matched sibling.
- Outcomes with alternative donor transplants are improving with regimens that should lead to fewer late effects.
- With improving outcomes with less toxic transplant, may want to consider alternative donor BMT earlier for patients not having a good initial response to ATG.

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## SAA: Common Practical Questions?

- Can this disease be fatal?
  - Yes
  - Death due to invasive fungal infections or bleeding.
  - As the data shows, many people will survive.

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## SAA: Common Practical Questions?

- Where can I turn to learn more?
  - Aplastic Anemia & MDS International Foundation
  - [www.aamds.org](http://www.aamds.org)



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### SAA: Common Practical Questions?

- When should we give RBC transfusions?
  - When you need to.
  - Hemoglobin around 6 g/dl.
  - Irradiated, Filtered, CMV negative.

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### SAA: Common Practical Questions?

- When should we chelate?
  - Liver biopsy is "gold standard"
  - MRI may replace liver biopsy.
  - Ferritin above 1500-2000
  - Oral chelator: Exjade (deferasirox)

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### SAA: Common Practical Questions?

- When should we give platelet transfusions?
  - When the patient has symptoms.
  - 5-10K
  - Single Donor Pheresis Product
  - Irradiated, Filtered, CMV negative

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## SAA: Common Practical Questions?

- What is the role for GCSF?
  - No data suggests it leads to a response.
  - Some data suggesting ANC >500 will help prevent invasive fungal infections.
  - I try to keep ANC >500 with as little GCSF as possible.

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## SAA: Common Practical Questions?

- Can my child go to school?
  - I think so.
  - Infection risk at school is primarily virus based.
  - Viruses can slow down recovery, so I leave it up to parents.

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