Severe Aplastic Anemia

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Pediatric BMT
Medical College of Wisconsin
Outline of Talk

1. Clinical description of aplastic anemia
2. Data collection forms

And a couple of quizzes in between...
What is aplastic anemia?

• More than just anemia
  – Involves low counts in 2 of 3 cell lines: red blood cells (RBC), white blood cells (WBC), platelets
• Should NOT involve dysplasia
  – Exception: RBC can sometimes be dysplastic
• Should have NORMAL cytogenetics
• If dysplasia (beyond RBCs) or abnormal cytogenetics seen, think myelodysplastic syndrome (MDS)
What is “severe” aplastic anemia?

- Marrow cellularity $\leq 25\%$ AND
- Two of the following peripheral blood features:
  - Absolute neutrophil count (ANC) $< 0.5 \times 10^9$/L
  - Platelet count $< 20 \times 10^9$/L
  - Absolute reticulocyte count $< 40 \times 10^9$/L

- “Very” severe aplastic anemia
  - Same as above except ANC $< 0.2 \times 10^9$/L
Bottom Line:
Severely Reduced Hematopoietic Stem Cell Precursors In Bone Marrow
Epidemiology

• Half of cases seen in first 3 decades of life
• Incidence:
  – 2 cases/million in Western countries
  – 2-3 fold higher in Asia
• Ethnic predisposition:
  – Asian
    • Genetics vs different environmental exposures?
• Sex predisposition: M:F is 1:1
Pathophysiology: 3 Main Mechanisms Proposed

1. Immune-mediated
   - **Hypothesis**: Revved-up T cells destroy stem cells
   - **Observation**: Immunosuppression improves blood counts

2. Stem-cell “depletion” or “defect”
   - **Hypothesis**: Drugs or viruses directly destroy stem cells
   - **Observation**: Syngeneic transplants without prior conditioning can cure disease

3. Abnormal marrow microenvironment (less likely cause)
   - **Hypothesis**: The marrow niche cannot support stem cells
   - **Observation**: Long-term culture of stromal cells from aplastic anemia patients can sometimes be difficult
Causes of Aplastic Anemia

- **Number 1 Cause: Idiopathic (unknown)**
- Ionizing radiation
- Drugs
  - Chloramphenicol
  - Phenylbutazone
  - Sulfonamides
  - Gold
  - Certain anticonvulsants (felbamate, carbamazepine)
  - Quinine
- Genetic disorders
  - Fanconi Anemia
  - Dyskeratosis congenita
  - *Diamond-Blackfan anemia*
  - *Shwachman-Diamond Syndrome*
- Viruses
  - Non-A, B, C Hepatitis
  - Parvovirus
  - Epstein-Bar Virus
- Autoimmune
  - Eosinophilic fasciitis
- Pregnancy
Clinical Presentation

- Low RBC
  - Pallor
  - Fatigue
  - Exercise intolerance/heart failure

- Low Platelets
  - Bleeding
  - Bruising

- Low WBC
  - Infections
Work-up and Evaluation

- CBC
- Reticulocyte count
- Bone marrow aspirate
  - Morphology
  - Cytogenetics
- Bone marrow biopsy
- Rule-out other disorders
  - Fanconi Anemia: chromosomal fragility (DEB/MMC)
  - Dyskeratosis congenita: short telomeres
  - Diamond-Blackfan Anemia: gene mutations (RPS19)
  - Shwachman-Diamond Syndrome: gene mutation (SBDS)
  - Paroxysmal Nocturnal Hemoglobinuria: flow cytometry (CD55/59)
Treatment of Aplastic Anemia

• Immunosuppression
  – Gold standard: Anti-thymocyte globulin (ATG) and cyclosporine (CSP)
  – 2/3 of patients will initially respond
    • Response is typically NOT complete
  – Concerns: 1) Frequently not a durable solution
    2) Risk of infectious complications

• G-CSF (+ Immunosuppression)
  – Controversial; conflicting reports of benefit
  – Concern: Reports of transformation to MDS/AML

• Transfusion support
  – Rapid results for life-threatening anemia or bleeding
  – Concerns: 1) Not a durable solution
    2) Risk of antibody development--multiple-donor transfusions
    3) Risk or iron overload
Role of Transplantation for Aplastic Anemia

• Objective: Replace non-functional marrow with functioning marrow

• Indications for transplantation:
  – Matched-sibling donor
  – Refractory to immunosuppressive therapy
  – Transfusion dependence
  – Iron overload
  – Life-threatening bleeding
  – Life-threatening infections
What can Aplastic Anemia be confused for?

- Myelodysplastic syndrome
- Recovering marrow from chemotherapy
- Early presentation of leukemia

How can these entities be distinguished?

- Look at the time-line
  - What is the temporal relationship to chemotherapy?
- Evaluate bone marrow aspirate
  - Is there dysplasia and/or abnormal cytogenetics?
  - Are there hematopoietic precursors?
Can aplastic anemia be a predisposing condition for developing AML or MDS?

• YES! But overall a rare phenomenon
• May be due to prior therapy
  – Immunosuppression
  – Hematopoietic cell transplantation
• Why is this important to know?
  – Will affect which CIBMTR forms to fill out
Quick Quiz

1. A patient with aplastic anemia undergoes a marrow transplant. After transplant, she is still anemic and thrombocytopenic.

a) She is still recovering from her transplant -- give her time

b) Her transplant has failed and she still has aplastic anemia
Quick Quiz

2. After finishing his third round of chemotherapy, a patient with AML has developed prolonged neutropenia. He undergoes a marrow aspirate that shows decreased WBC and RBC precursors.
   a) He has now developed aplastic anemia
   b) He has now developed MDS
   c) He has now developed recurrent AML
   d) He is still recovering counts—give him time
DATA COLLECTION
Data collection: Critical Points

- Date of diagnosis
- Pre-transplant co-morbidities
- Prior therapy
- Lab work that confirms diagnosis
CIBMTR Forms to Fill Out for Aplastic Anemia

Aplastic Anemia-specific forms:
1. Form 2028 (APL): Aplastic Anemia Pre-HSCT Data
2. Form 2128 (APL): Aplastic Anemia Post-HSCT Data

Also need to fill out:
1. Form 2000 (All diseases): Recipient Baseline Data
2. Form 2100 (All diseases): 100 Days Post-HSCT Data

May need to fill out:
1. Form 2014/2114 (MDS): Myelodysplasia /Myeloproliferative Disorders Pre-HSCT Data/Post-HSCT Data
2. Form 2010/2110 (AML): Acute Myelogenous Leukemia Pre-HSCT Data/Post-HSCT Data
Form 2028 (APL): Aplastic Anemia Pre-HSCT Data (1)

Disease Assessment at Diagnosis

1. What was the date of diagnosis of Aplastic Anemia? [ ] [ ] [ ] [ ]

2. Was the recipient's bone marrow examined at diagnosis?
   1. yes  
   2. no  
   3. unknown

   3. Is a copy of the biopsy report attached?
      1. yes  
      2. no

4. Were the recipient's cells tested for sensitivity to cross-linking agents (e.g., diepoxybutane (DEB), mitomycin C (MMC))? 
   1. yes  
   2. no  
   3. unknown

   5. Specify the test results:
      1. normal
      2. increased chromosome breaks
      3. unknown

   6. Is a copy of the test report attached?
      1. yes  
      2. no
Form 2028 (APL): Aplastic Anemia Pre-HSCT Data (1)

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Date of marrow that diagnosed SAA (or date that MD states SAA developed if source document not available)
**Form 2028 (APL): Aplastic Anemia Pre-HSCT Data (1)**

### Disease Assessment at Diagnosis

1. What was the date of diagnosis of Aplastic Anemia?
   - [ ] Month
   - [ ] Day
   - [ ] Year

2. Was the recipient's bone marrow examined at diagnosis?
   - [ ] yes
   - [ ] no
   - [ ] unknown

   Is a copy of the biopsy report attached?
   - [ ] yes
   - [ ] no

3. Were the recipient's cells tested for sensitivity to DNA-interlinking agents (e.g., diepoxybutane (DEB), mitomycin C (MMC))?
   - [ ] yes
   - [ ] no
   - [ ] unknown

4. Specify the test results:
   - [ ] normal
   - [ ] increased chromosome break
   - [ ] unknown

5. Is a copy of the test report attached?
   - [ ] yes
   - [ ] no

**ATTACH THE REPORT if available!**
This will save a future data manager from sifting through old charts in the future!
Form 2028 (APL): Aplastic Anemia Pre-HSCT Data (2)

7. What was the disease etiology?
   1. Diamond-Blackfan anemia
   2. drug induced
   3. viral hepatitis
   4. idiopathic
   5. other

8. Specify drug: ________________________ □ drug unknown
9. Specify type: ________________________ □ type unknown
10. Specify disease etiology: ________________________ □ etiology unknown

11. Was testing for paroxysmal nocturnal hemoglobinuria (PNH) performed?
   1. yes
   2. no
   3. unknown

Specify PNH test and results:
12. 1 □ positive 2 □ negative 3 □ unknown Flow cytometry for CD55 / CD16 / CD59
13. 1 □ positive 2 □ negative 3 □ unknown Ham's acid hemolysis test
14. 1 □ positive 2 □ negative 3 □ unknown Hemosiderinuria
15. 1 □ positive 2 □ negative 3 □ unknown PIGA GPI anchor protein defect
16. 1 □ positive 2 □ negative 3 □ unknown Sugar water / sucrose lysis test
17. 1 □ positive 2 □ negative 3 □ unknown Other test
18. Specify test: ________________________
Form 2028 (APL): Aplastic Anemia Pre-HSCT Data (2)

7. What was the disease etiology?
   1. Diamond-Blackfan anemia
   2. drug induced
   3. viral hepatitis
   4. idiopathic
   5. other

8. Specify drug: ____________
9. Specify type: ____________
10. Specify disease etiology: ____________

Sometimes the etiology is known (frequently it is not!) Fill in what is known.

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   1. yes
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18. Specify test: ____________
Laboratory Studies at Diagnosis
Report findings prior to any first treatment for aplastic anemia.

19. WBC:
   1. known
   2. not known

20. Hemoglobin:
   1. known
   2. not known

21. Was RBC transfused < 30 days before date of test?
   1. yes
   2. no

22. Platelets:
   1. known
   2. not known

23. Were platelets transfused < 7 days before date of test?
   1. yes
   2. no

24. Neutrophils:
   1. known
   2. not known

25. Reticulocytes (uncorrected):
   1. known
   2. not known

Specify units:
1. x 10^9/L (x 10^3/mm^3)
2. x 10^6/L
1. g/dL
2. g/L
3. mmol/L
1. x 10^9/L (x 10^3/mm^3)
2. x 10^6/L
10^9/L
10^9/L
Key word is 
DIAGNOSIS!
Form 2028 (APL): Aplastic Anemia Pre-HSCT Data (2)

**Laboratory Studies at Diagnosis**

Report findings prior to any first treatment for aplastic anemia.

<table>
<thead>
<tr>
<th>Test</th>
<th>Units Options</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>19. WBC</td>
<td>x $10^9/L$ (x $10^3$/mm$^3$)</td>
<td>1. x $10^9$/L 2. x $10^6$/L</td>
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<tr>
<td>20. Hemoglobin</td>
<td>g/dL</td>
<td>1. g/dL 2. g/L 3. mmol/L</td>
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<td>21. Was RBC transfused</td>
<td>&lt; 30 days before date of test</td>
<td>1. yes 2. no</td>
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<tr>
<td>22. Platelets</td>
<td>x $10^9/L$ (x $10^3$/mm$^3$)</td>
<td>1. x $10^9$/L 2. x $10^6$/L</td>
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<td>&lt; 7 days before date of test</td>
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<td>24. Neutrophils</td>
<td>x $10^9/L$</td>
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Pay attention to UNITS!
**Form 2028 (APL): Aplastic Anemia Pre-HSCT Data (2)**

### Laboratory Studies at Diagnosis

**Report findings prior to any first treatment for aplastic anemia.**

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**Specify units:**

1. $x \times 10^9$/L ($x \times 10^3$/mm$^3$)
2. $x \times 10^6$/L

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<th>20. Hemoglobin:</th>
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**Specify units:**

1. $x \times 10^9$/L ($x \times 10^3$/mm$^3$)
2. $x \times 10^6$/L

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**Important to know—**

1) transfusion dependence
2) counts may be inaccurate if pt was transfused
Form 2028 (APL): Aplastic Anemia Pre-HSCT Data (3)

26. Was therapy given for treatment of aplastic anemia prior to the start of the preparative regimen?
   1. Yes
   2. No
   3. Unknown

Specify what treatment(s) were given:
27. 1. Yes 2. No Androgens
28. 1. Yes 2. No ATG, ALS, ATS, ALG
29. 1. Yes 2. No Chelation therapy for iron
30. 1. Yes 2. No Corticosteroids
31. 1. Yes 2. No Cyclosporine (CsA, Neoral, Sandimmune)
32. 1. Yes 2. No Cytokines

If yes, specify cytokine(s) given:
33. 1. Yes 2. No Erythropoietin (EPO)
34. 1. Yes 2. No G-CSF (filgrastim, Neupogen)
35. 1. Yes 2. No GM-CSF (sargramostim, Leukine)
36. 1. Yes 2. No Interleukin-3 (IL-3)
37. 1. Yes 2. No Pegfilgrastim (Neulasta)
38. 1. Yes 2. No Stem cell factor (SCF)
39. 1. Yes 2. No Other

40. If yes, specify other cytokine:

41. 1. Yes 2. No Other immunosuppression

42. If yes, specify immunosuppression:

43. 1. Yes 2. No Other treatment

44. If yes, specify treatment:
Form 2028 (APL): Aplastic Anemia Pre-HSCT Data (3)

Transfusion Status from Diagnosis to the Start of the Preparative Regimen

45. Did the recipient receive red blood cell transfusions between diagnosis and the start of the preparative regimen?

1 □ yes
2 □ no

46. Specify the total number of donor exposures (best estimate):

1 □ 1–5
2 □ 6–10
3 □ 11–20
4 □ 21–30
5 □ 31–40
6 □ 41–50
7 □ ≥ 51
8 □ unknown

47. Did the recipient receive platelet transfusions between diagnosis and the start of the preparative regimen?

1 □ yes
2 □ no
Form 2028 (APL): Aplastic Anemia Pre-HSCT Data (3)

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Form 2028 (APL): Aplastic Anemia Pre-HSCT Data (3)

**Transfusion Status from Diagnosis to the Start of the Preparative Regimen**

45. Did the recipient receive red blood cell transfusions between diagnosis and the start of the preparative regimen?

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<tr>
<td>1</td>
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- 1: 1–5
- 2: 6–10
- 3: 11–20
- 4: 21–30
- 5: 31–40
- 6: 41–50
- 7: ≥ 51
- 8: unknown

This is asking for number of DONOR EXPOSURES (NOT number of transfusions). This comes into play if a patient received directed-donor transfusions.
Transfusion Status from Diagnosis to the Start of the Preparative Regimen

45. Did the recipient receive red blood cell transfusions between diagnosis and the start of the preparative regimen?

1. yes
2. no

46. Specify the total number of donor exposures (best estimate):

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- 4. 21-30
- 5. 31-40
- 6. 41-50
- 7. ≥ 51
- 8. unknown

47. Did the recipient receive platelet transfusions between diagnosis and the start of the preparative regimen?

1. yes
2. no

Just yes-no question when asking about platelet transfusions
Laboratory Findings Prior to the Start of the Preparative Regimen

48. Reticulocytes (uncorrected):
- [ ] known
- [x] not known

49. Date of most recent bone marrow biopsy:
   - Month
   - Day 20
   - Year
Form 2028 (APL): Aplastic Anemia Pre-HSCT Data (3)

**Laboratory Findings Prior to the Start of the Preparative Regimen**

48. Reticulocytes (uncorrected):
   - [ ] known
   - [x] not known

   

10⁹/L

49. Date of most recent bone marrow biopsy:
   - Month
   - Day
   - Year

[2][0][ ]

Units!
Form 2028 (APL): Aplastic Anemia Pre-HSCT Data (3)

Laboratory Findings Prior to the Start of the Preparative Regimen

48. Reticulocytes (uncorrected):
   1 □ known
   2 □ not known
   □ 10^9/L

49. Date of most recent bone marrow biopsy:
   □ Month □ Day □ Year

Make sure to record the BM biopsy CLOSEST to the start of the preparative regimen.
Form 2028 (APL): Aplastic Anemia Pre-HSCT Data (4)

50. Is a copy of the most recent bone marrow biopsy report attached?
   1 □ yes
   2 □ no

51. Were any clinically important infections present or being treated within one week prior to the preparative regimen?
   1 □ yes
   2 □ no
   3 □ unknown

<table>
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<tr>
<th>Organism ‡</th>
<th>Site *</th>
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‡ The codes for “other organism, specify” (codes 198, 209, 219, 259, 329 and 409) should rarely be needed; check with your microbiology lab or HSCT physician before using them.

* Do not report fever in the absence of infection. Report the most specific site of infection.
50. Is a copy of the most recent bone marrow biopsy report attached?
1. [ ] yes
2. [ ] no

51. Were any clinically important infections present or being treated within one week prior to the preparative regimen?
1. [ ] yes
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* Do not report fever in the absence of infection. Report the most specific site of infection.
Clinically important means:
1) An organism was found and treated
2) An organism was suspected and treated
3) A fever of unknown source occurred, but the patient improved on drug therapy
### Codes for Commonly Reported Organisms

<table>
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<tr>
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<td>198</td>
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</tr>
<tr>
<td>501</td>
<td>Suspected atypical bacterial infection</td>
</tr>
<tr>
<td>502</td>
<td>Suspected bacterial infection</td>
</tr>
<tr>
<td>259</td>
<td>Other fungus, specify</td>
</tr>
<tr>
<td>503</td>
<td>Suspected fungal infection</td>
</tr>
<tr>
<td>329</td>
<td>Other virus, specify</td>
</tr>
<tr>
<td>504</td>
<td>Suspected viral infection</td>
</tr>
<tr>
<td>409</td>
<td>Other parasite, specify</td>
</tr>
<tr>
<td>505</td>
<td>Suspected parasite infection</td>
</tr>
</tbody>
</table>

### Other Infections

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>509</td>
<td>No organism identified</td>
</tr>
</tbody>
</table>
Summary: Areas of concern on Pre-HSCT forms

- Correct date of diagnosis
- Attaching BM biopsy reports when available
- Recording the correct “start of preparative regimen” lab values
  - These are usually not the same as the lab values at time of diagnosis
- A fever by itself does not count as a “clinically important” infection
Form 2128 (APL): Aplastic Anemia Post-HSCT Data (1)

Visit: □ 100 day □ 6 month □ 1 year □ 2 years □ > 2 years, specify: □ □
### Disease Status at the Time of Assessment for This Reporting Period

1. Was the recipient red blood cell (RBC) transfusion independent since the date of the last report?
   - □ yes
   - □ no
   - □ unknown

2. Date of the most recent RBC transfusion: *
   - Month
   - Day
   - Year
   * If the recipient was RBC transfusion independent for ≥ one month but subsequently experienced a decline in RBCs and required transfusions, record the date of the last RBC transfusion before the decline. If the recipient has not required any transfusions since the initial date of recovery, record the date of the last RBC transfusion.

3. Was the recipient platelet transfusion independent since the date of the last report?
   - □ yes
   - □ no
   - □ unknown
   - □ not applicable / never dependent

4. Date of the most recent platelet transfusion: *
   - Month
   - Day
   - Year
   * If the recipient was platelet transfusion independent for ≥ 14 days but subsequently experienced a decline in platelets and required transfusions, record the date of the last platelet transfusion before the decline. If the recipient has not required any transfusions since the initial date of recovery, record the date of the last platelet transfusion.

5. Specify reticulocyte level (uncorrected):
   - □ known
   - □ not known / transfused
   - □ 10⁹/L
Additional forms you *may* need to fill out

1. Form 2014/2114 (MDS): Myelodysplasia / Myeloproliferative Disorders Pre-HSCT Data/Post-HSCT Data

1. Form 2010/2110 (AML): Acute Myelogenous Leukemia Pre-HSCT Data/Post-HSCT Data
11. Did the recipient have other predisposing conditions prior to diagnosis of the hematologic disorder?
   1. □ yes
   2. □ no

12. Specify predisposing condition:
   1. □ aplastic anemia
   12. Specify predisposing condition:
   
13. Did the recipient have a predisposing condition prior to the diagnosis of leukemia?
   1. □ yes
   2. □ no

14. Specify condition:
   1. □ aplastic anemia
   
Also complete Form 2028 — APL

Also complete CIBMTR Form 2028 — APL
Rationale for Future Research

- These forms may change over time based on research directions of CIBMTR
- Important to attach reports even when optional to aid in data gathering for future research questions
Quick Quiz

1. A patient develops aplastic anemia and is treated with immunosuppression only with good response. Two years into therapy, the patient develops secondary AML and goes to transplant as a result. How do you report this to the CIBMTR?
   a) Use the insert form for Aplastic Anemia only
   b) Use the insert form for AML only
   c) Use both Aplastic Anemia and AML insert forms
2. A patient develops severe aplastic anemia and is transplanted. Six months after transplant, the patient develops secondary MDS. How do you report this to the CIBMTR?

a) Pre-transplant: Aplastic Anemia insert
   Post-transplant: Aplastic Anemia insert

b) Pre-transplant: Aplastic Anemia insert
   Post-transplant: MDS insert
3. Let’s say that this last patient who developed secondary MDS now goes on to have a second transplant. How do you report this to the CIBMTR?

a) Pre-transplant #2: Aplastic Anemia insert  
   Post-transplant #2: MDS insert

b) Pre-transplant #2: MDS insert  
   Post-transplant #2: MDS insert
Thank you for your attention!

Questions?