Objectives

• Review the epidemiology, clinical presentation and diagnosis of aplastic anemia in adults

• Discuss the therapy of aplastic anemia in adults
Introduction

• Bone marrow failure syndrome
  – pancytopenia
  – bone marrow hypocellularity

• First described by Paul Ehrlich in 1888
Introduction

• Epidemiology
  – likely ~ 2/million in Western populations
    • Studies from Spain, France, UK, Scandinavia and Brazil
  
  – higher incidence in Asia

  – gender ratio 1:1

  – 2 age peaks
    • young adults, elderly
## Incidence of Aplastic Anemia, Spain

<table>
<thead>
<tr>
<th>Age at diagnosis (years)</th>
<th>2-14</th>
<th>15-24</th>
<th>25-44</th>
<th>45-64</th>
<th>≥65</th>
<th>N. of cases</th>
<th>Total incidence(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Male</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N. of cases</td>
<td>17</td>
<td>25</td>
<td>22</td>
<td>28</td>
<td>31</td>
<td>123</td>
<td></td>
</tr>
<tr>
<td>Incidence</td>
<td>1.92</td>
<td>2.83</td>
<td>1.52</td>
<td>2.56</td>
<td>5.89</td>
<td>2.54</td>
<td></td>
</tr>
<tr>
<td><strong>Female</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N. of cases</td>
<td>12</td>
<td>11</td>
<td>15</td>
<td>31</td>
<td>43</td>
<td>112</td>
<td></td>
</tr>
<tr>
<td>Incidence</td>
<td>1.43</td>
<td>1.41</td>
<td>1.00</td>
<td>2.58</td>
<td>4.89</td>
<td>2.16</td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N. of cases</td>
<td>29</td>
<td>36</td>
<td>37</td>
<td>59</td>
<td>74</td>
<td>235</td>
<td></td>
</tr>
<tr>
<td>Incidence</td>
<td>1.68</td>
<td>2.16</td>
<td>1.26</td>
<td>2.57</td>
<td>5.33</td>
<td>2.34</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\)Number of cases per one million people per year.

Clinical Presentation

• Secondary to decreased blood cells
  – anemia (low red cells)
    • fatigue, chest pain and shortness of breath with exertion, palpitations
  – thrombocytopenia (low platelets)
    • bleeding, bruising, petechiae
  – leukopenia (low white blood cells)
    • infections
Approach to Aplastic Anemia

• Confirmation of the diagnosis

• Define the disease
  – acquired or congenital
  – cause
  – disease severity
Approach to Aplastic Anemia

• Traditional definition
  – pancytopenia with hypocellular bone marrow
  – normal hematopoietic tissue replaced by fat cells
  – absence of abnormal infiltrate in the bone marrow or increased reticulin (fibrosis or scar)
  – at least 2 of hemoglobin < 100 g/L, platelets < 100, absolute neutrophil count < 1500
Approach to Aplastic Anemia
Approach to Aplastic Anemia

• Is the diagnosis really aplastic anemia?
  – Exclude:
    • hypocellular MDS
    • myelofibrosis
    • lymphoma
    • atypical mycobacterial infection
    • anorexia nervosa
Approach to Aplastic Anemia

• Is the disease an inherited bone marrow failure syndrome?
  – Fanconi anemia
  – Dyskeratosis congenita
  – Shwachman-Diamond syndrome
Approach to Aplastic Anemia

• What is the cause?
  – idiopathic
  – post-hepatitic
  – drugs, chemicals, environmental exposures
  – PNH
  – pregnancy
  – thymoma
Approach to Aplastic Anemia

• How severe is the disease?
  – Severe aplastic anemia
    • Bone marrow cellularity < 25%
    • 2/3: ANC < 500, platelets < 20, reticulocytes < 20

  – Very severe aplastic anemia
    • As above except ANC < 200

Adapted from Marsh ASH Education
2006
What is the cause of idiopathic aplastic anemia?

• Immune mediated disease

• Variability
  – environmental exposures
  – patient risk factors
  – differences in immune response
Immune destruction of hematopoiesis

Treatment

• Depends on severity of disease
  – Nonsevere aplastic anemia
    • follow expectantly
  – Severe aplastic anemia
    • immunosuppression versus allogeneic bone marrow transplant
Immunosuppression

• Reducing the activation or effectiveness of the immune system

• If aplastic anemia is an autoimmune disease, “shutting down” the immune system is logical
Immunosuppression

• Standard therapy
  – antithymocyte globulin (ATG) and cyclosporin
Immunosuppression

• ATG
  – injection of human lymphocytes into an animal
  – animal makes antibodies against the lymphocytes
  – the antibodies attack the lymphocytes in the patient
ATG

• Side effects
  – allergic reaction
  – cytokine release syndrome
  – serum sickness
  – infections
Cyclosporin

- Inhibits T lymphocytes

- Side effects
  - kidney problems
  - high blood pressure
  - metabolic problems
  - infections
# Immunosuppression

<table>
<thead>
<tr>
<th>Study Group</th>
<th>N</th>
<th>Median Age</th>
<th>Response (%)</th>
<th>Relapse (%)</th>
<th>Clonal Evolution (%)</th>
<th>Survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>German</td>
<td>84</td>
<td>32</td>
<td>65</td>
<td>19</td>
<td>8</td>
<td>58(11 yrs)</td>
</tr>
<tr>
<td>EGBMT</td>
<td>100</td>
<td>16</td>
<td>77</td>
<td>12</td>
<td>11</td>
<td>87(5 yrs)</td>
</tr>
<tr>
<td>NIH</td>
<td>122</td>
<td>35</td>
<td>61</td>
<td>35</td>
<td>11</td>
<td>55(7 yrs)</td>
</tr>
<tr>
<td>Japan</td>
<td>119</td>
<td>9</td>
<td>68</td>
<td>22</td>
<td>6</td>
<td>88(3 yrs)</td>
</tr>
<tr>
<td>NIH</td>
<td>104</td>
<td>30</td>
<td>62</td>
<td>37</td>
<td>9</td>
<td>80(4 yrs)</td>
</tr>
</tbody>
</table>

Adapted from Young et al Blood 2006
Late Events After Immunosuppressive Therapy

Relapse after ATG + Cyclosporin

• High risk of relapse
  – 20-40%

• Treat with second course of ATG
  – 50-60% will respond to second course

• No prospective trial comparing horse to rabbit ATG; choice depends on:
  – whether a severe reaction occurred with first course
  – centre practice
  – drug availability
Bone Marrow Transplant

• Background
  – curative therapy

  – 1961
    • first successful transplant using a syngeneic (identical twin) donor
  – 1972
    • first successful transplant using a matched, unrelated donor
  – 1976
    • randomized prospective trial showed survival advantage of matched related donor over standard of care
Bone Marrow Transplant

- Transplanted bone marrow stem cells replaces the failing bone marrow cells

- Stem cells reconstitute all the normal cells
  - new immune system
  - new red cells
  - new platelets
Bone Marrow Transplant

- Potential cure but...

- Complications
  - side effects from chemotherapy
  - graft rejection
  - graft versus host disease
  - long term complications
Bone Marrow Transplant

• Acute complications
  – nausea, vomiting, diarrhea, mucositis
  – organ damage
  – infections
  – bleeding
Bone Marrow Transplant

• Graft failure
  – central problem in aplastic anemia
  – reported in up to 5-15% of patients

  – why?
    • conditioning regimens are nonmyeloablative
      (chemotherapy not as strong as other transplants)
    • immune activity rejects the graft
Bone Marrow Transplant

• Graft versus host disease
  – acute versus chronic
  • At least 20-40% of patients

  – can be difficult to treat and associated with significant morbidity and decreased quality of life
Long-term Complications

- Toxicities from treatment regimens
- Immune deficiency
- Autoimmune syndromes
- Infectious complications
- Endocrine disturbances
- Chronic GVHD
- Second malignancies
- Cognitive dysfunction
- Psychosocial adjustment
- Decreased quality of life
Bone Marrow Transplant

• Source of stem cells
  – unmanipulated bone marrow first choice

  – peripheral blood stem cells
    • faster engraftment, but increased GVHD and lower survival

  – umbilical cord blood
    • little data
Syngeneic Allogeneic BMT

• Ideal donor is an identical twin
  – no need for graft versus tumor effect
  – minimizes risk of graft failure
  – no GVHD

  – survival rates of 70-90%
Sibling Allogeneic BMT

• Few prospective studies

• Important to consider sibling BMT early

• Steady improvement in outcome over time
Sibling Allogeneic BMT
Sibling BMT compared to Immunosuppression

Effect of patient age on survival by treatment group

Sibling Allogeneic BMT

• Recommendations
  – younger adults with a sibling donor should be treated with allogeneic BMT over immunosuppressive therapy
  – transfusions prior to transplant should be minimized
  – conditioning generally with cyclophosphamide + ATG
Matched, unrelated BMT

- Little prospective data
- Higher morbidity and mortality than sibling BMT
- Improved survival over time
Impact of Better HLA Matching in MUD BMT

Matched, unrelated BMT

• Recommendations
  – at least 2 courses of immunosuppression should be given before considering proceeding with a MUD BMT
Approach to Treatment

1. Excluded inherited bone marrow failure syndrome
2. If disease progression to severe AA, follow algorithm for SAA
3. Red cell and/or platelet transfusion dependent

- No
  - Observe and monitor FBC, or treat if patient's lifestyle dictates
- Yes
  - If become transfusion dependent
    - ATG(horse)+CSA
      - Response at 4 months
        - No
          - 2nd ATG (rabbit/horse)+CSA
            - No response at 4 months
              - Follow algorithm for severe AA
        - Yes
          - Maintain CSA as for severe AA

Marsh, J. Hematology 2006;2006:78-85
Approach to Treatment

Age of patient

≤ 40yr
- HLA identical sibling
  - Yes: HLA id sib BMT
  - No: ATG (horse)+CSA

Response at 4 months
- Yes: Maintain on CSA while FBC rising, then very slow taper, often over one/more years
- No: 2nd ATG (rabbit/horse) + CSA

Response at 4 months
- Yes: MUD available
  - No: Adequate performance status
    - Yes: Adequate performance status
    - No: Supportive therapy
      - Yes: MUD BMT
      - No: Options

1. 3rd ATG if previous response to ATG
2. CRP using novel IST
3. BMT using CRP with UCB

Marsh, J. Hematology 2006;2006:78-85
• Thank you!

• Questions?