Pulmonary Complications of Bone Marrow Transplantation:
When infection isn’t the answer

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PGY-2 Critical Care Resident
Objectives

• List the American Thoracic Society diagnostic criteria for idiopathic pneumonia syndrome

• Identify key clinical differences between diffuse alveolar hemorrhage, peri-engraftment respiratory distress syndrome, and non-cardiogenic capillary leak syndrome

• Determine the role of corticosteroid therapy in treatment of diffuse alveolar hemorrhage
65 y/o M with respiratory distress

• Past Medical History:
  • Type II Diabetes Mellitus
  • Atrial fibrillation
  • Anxiety/depression
  • Myelodysplastic syndrome (MDS)

- 10/2011: Biopsy, MDS
- 7/2012: 5-azacitidine
- 9/2014: Decitabine x7 cycles
- 7/2015: Cyclosporine + prednisone
History of Present Illness

Day -6:
- Conditioning regimen: fludarabine, melphalan

Day 0:
- Allogeneic, peripheral blood stem cell transplant

Day +8:
- Hospital admission
- Mucositis
- ANC: 0 cells/μL

Day +16:
- Transferred to ICU
- Increased WOB
- ANC: 280 cells/μL

ANC: absolute neutrophil count
WOB: work of breathing
Idiopathic Pneumonia Syndrome

- Peri-engraftment respiratory distress syndrome
- Non-cardiogenic capillary leak syndrome
- Diffuse alveolar hemorrhage
- Cryptogenic organizing pneumonia
- Delayed pulmonary toxicity syndrome
- Bronchiolitis obliterans syndrome

Pathophysiology

- Inflammatory cytokines
- Previous infections
- Conditioning chemotherapy
- Total body irradiation
- T-cell activation

Alveolus

Capillary

Pathophysiology, Example: DAH

Inflammatory cytokines

Previous infections

Conditioning chemotherapy

Total body irradiation

T-cell activation

Alveolus

Capillary

Pathophysiology

IPS: American Thoracic Society Definition

1. Evidence of widespread alveolar injury
2. Absence of infection
3. Absence of cardiac dysfunction, acute decline in renal function as a sole explanation

Where do we go from here?

Back to the Case

• Vital signs
  • T 39.0°C
  • SaO₂: 88%
  • RR: 28
  • HR: 112 bpm
  • BP: 151/72 mmHg

• Physical exam: notable for bilateral lower extremity edema

• Blood cultures, tracheal secretions pending

• Chest x-ray
Bilateral, Multi-lobar Pulmonary Infiltrates
Back to the Case

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- Considering CT chest, BAL
Respiratory distress in a BMT patient

Infection?

- Work-up ongoing
- Initiated on broad spectrum antibiotics

Timeline

Days 1-30:
- Diffuse alveolar hemorrhage
- Peri-engraftment respiratory distress syndrome
- Non-cardiogenic capillary leak syndrome

Days 100+:
- Delayed pulmonary toxicity syndrome
- Bronchiolitis obliterans syndrome
- Cryptogenic organizing pneumonia

DAH:
- Fever +/-
- Hemoptysis (~60%)
- Diagnosis: BAL
  - Progressively bloody return
  - >20% Hemosiderin-laden macrophages

PERDS:
- Fever
- Cutaneous rash
- Days surrounding engraftment

CLS:
- i.e., pulmonary edema
- Weight gain
- Peripheral edema
  - Responsive to diuresis

Respiratory distress
Back to the Case: What’s the Verdict?

• PERDS
  ✓ Previous day, first detectable ANC
  ✗ No rash on physical exam

• CLS
  ✗ Down 2kg from admission
  ✓ Peripheral edema on physical exam

• DAH
  ✓ Progressively bloody return on BAL
  ✓ 26% hemosiderin-laden macrophages
Diffuse Alveolar Hemorrhage

• Epidemiology:
  • Median onset day +19 (range, day +5-34)
  • 5-12% incidence in BMT population
  • Reported 21-day mortality 60-100%

• Risk factors:
  • Age >40 years
  • Full-intensity conditioning regimen, total body irradiation
  • Underlying acute leukemia or MDS
  • Type of transplant?

• PT/PTT, thrombocytopenia are **NOT** risk factors

Diffuse Alveolar Hemorrhage

Use of Corticosteroids in Bone Marrow Transplant Patients
Treatment Outline

1. Steroids
2. Steroids
3. Steroids
Diffuse Alveolar Hemorrhage

Immune Mediated
- ANCA-associated vasculitis
- Systemic lupus erythematosus
- Rheumatoid arthritis
- Antiphospholipid antibody syndrome

Non-Immune Mediated
- Infection
- Acute respiratory distress syndrome
- Coagulopathy
- Left ventricular dysfunction

Pathophysiology

Alveolus

Capillary

Treatment Outline

1. Steroids
2. Steroids
3. Steroids
4. Others?
   • Management of coagulopathy
   • rVIIa
   • Etanercept

Let’s take a walk down memory lane…
Metcalf, et al.

- Retrospective cohort, descriptive analysis
- Patient population
  - January 3, 1985 – November 9, 1990
  - 603 BMT patients reviewed for DAH diagnosis
- Treatment (N = 63; 3 groups)
  - No steroids
  - Low-dose: ≤ 30mg methylprednisolone or equivalent
  - High-dose: > 30mg methylprednisolone or equivalent (125-250mg q6h)
Mortality

<table>
<thead>
<tr>
<th></th>
<th>No steroids (N = 12)</th>
<th>Low-dose (N = 10)</th>
<th>High-dose (N = 43)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death prior to discharge</td>
<td>11</td>
<td>9</td>
<td>29</td>
<td>P &lt;0.05</td>
</tr>
</tbody>
</table>

# Mortality

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<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death (at study conclusion?)</td>
<td>11</td>
<td>9</td>
<td>35</td>
</tr>
</tbody>
</table>

Mortality: Kaplan-Meier Curve

Study Conclusions

• Three different representations of mortality
  • Somewhat contradicting, confusing
  • Statistical methods unclear

• Difficult to interpret
  • Only available data
  • Doesn’t seem harmful? – ADE not well reported
  • Let’s go with it…
Raptis, et al.

• Retrospective case-series

• Patient population
  • September 1993 – January 1998
  • 74 BMT patients evaluated, 4 with DAH

• Treatment

<table>
<thead>
<tr>
<th>Case</th>
<th>#1</th>
<th>#2</th>
<th>#3</th>
<th>#4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methylprednisolone</td>
<td>1g daily</td>
<td>1g daily</td>
<td>2g x1, 1g daily</td>
<td>0.5g daily</td>
</tr>
<tr>
<td>regimen</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Study Conclusions

• 50% mortality due to DAH-related complications

• Authors’ perspective:
  • DAH is life-threatening
  • Potentially reversible with high-dose steroid treatment

• Even smaller population

• Again, doesn’t seem harmful?

Rathi, et al.

- Retrospective cohort, descriptive analysis

- Inclusion:
  - October 2007 – June 2011
  - BMT patients w/ DAH that received steroids +/- aminocaproic acid

- Exclusion:
  - Age <18 years
  - Steroids +/- aminocaproic acid for non-DAH illnesses
Treatment

BMT + DAH
n = 119

Steroids only
n = 37

- Low dose: <0.25 g/d
  n = 18
- Medium dose: 0.25-<1 g/d
  n = 11
- High dose: ≥1 g/day
  n = 8

Steroids + ACA
n = 82

- Low dose: <0.25 g/d
  n = 19
- Medium dose: 0.25-<1 g/d
  n = 50
- High dose: ≥1 g/day
  n = 23

## Mortality

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Low-dose</th>
<th>Medium-dose</th>
<th>High-dose</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Steroids only</strong></td>
<td>n = 18</td>
<td>n = 11</td>
<td>n = 23</td>
<td></td>
</tr>
<tr>
<td>Mortality – n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICU</td>
<td>4 (22.4)</td>
<td>7 (63.6)</td>
<td>6 (75)</td>
<td>0.02</td>
</tr>
<tr>
<td>Hospital</td>
<td>9 (50)</td>
<td>9 (81.8)</td>
<td>8 (100)</td>
<td>0.02</td>
</tr>
<tr>
<td><strong>Steroids + ACA</strong></td>
<td>n = 19</td>
<td>n = 40</td>
<td>n = 23</td>
<td></td>
</tr>
<tr>
<td>Mortality – n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICU</td>
<td>6 (31.6)</td>
<td>23 (57.5)</td>
<td>15 (65.2)</td>
<td>0.07</td>
</tr>
<tr>
<td>Hospital</td>
<td>13 (68.4)</td>
<td>33 (82.5)</td>
<td>18 (78.3)</td>
<td>0.45</td>
</tr>
</tbody>
</table>

*No difference when evaluating 30-d, 60-d, and 100-d mortality between steroid doses

A Closer Look…

<table>
<thead>
<tr>
<th>Variables</th>
<th>ICU Mortality</th>
<th>Hospital Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Steroids + ACA vs. steroids alone</td>
<td>0.81</td>
<td>0.29-2.27</td>
</tr>
<tr>
<td>Medium-dose vs. low-dose steroids</td>
<td>3.93</td>
<td>1.31-11.77</td>
</tr>
<tr>
<td>High-dose vs. low-dose steroids</td>
<td>4.79</td>
<td>1.45-15.90</td>
</tr>
</tbody>
</table>

*No difference when evaluating 30-d, 60-d, and 100-d mortality between groups

Study Conclusions

• Strongest study published – both size, design
  • Limitations still exist

• No benefit conferred with ACA
  • Makes sense, DAH not thought to be a result of coagulopathy

• Medium-, high-dose steroids potentially harmful

• No benefit in any group beyond hospital stay
Mortality: Kaplan-Meier Curve

Study Conclusions

• Strongest study published – both size, design
• No benefit conferred with ACA
  • Makes sense, DAH not thought to be a result of coagulopathy
• Medium-, high-dose steroids potentially harmful
• No benefit in any group beyond hospital stay
Harmful Effects of Steroids

- Not well described in aforementioned literature
- Infection
- Blood glucose control
- Delirium
- Myopathy
- Concurrent use of paralytic
Clinical Practice

• Clinicians recognize high risk for mortality
• Data scarce, conflicting
• Mayo Clinic – Rochester practice
  • Supportive cares + steroids
  • Methylprednisolone 250mg q6h x4-5 days followed by taper
  • Monitor for ADE, check in the ‘con’ column for considering short course
• Should practice shift away from the use of high-dose steroids?
Conclusion

- List the American Thoracic Society diagnostic criteria for idiopathic pneumonia syndrome
- Identify key clinical differences between diffuse alveolar hemorrhage, peri-engraftment respiratory distress syndrome, and non-cardiogenic capillary leak syndrome
- Determine the role of corticosteroid therapy in treatment of diffuse alveolar hemorrhage
Which of the following is true?

A. Use of aminocaproic acid for the treatment of DAH is the standard of care as it has been shown to significantly reduce 60-d mortality

B. Mortality associated with DAH s/p BMT is reported to be <10%

C. Treatment of DAH with steroids is controversial as studies have shown both positive and negative results

D. None of the above are true
JW is a 38y/o M s/p allogeneic PBSCT in the setting of ALL. He presents to the ICU day +14 with acute respiratory distress, a fever, and a diffuse cutaneous rash. What non-infectious pulmonary complication s/p BMT might JW be experiencing?

A. Diffuse alveolar hemorrhage
B. Cryptogenic organizing pneumonia
C. Non-cardiogenic capillary leak syndrome
D. Peri-engraftment respiratory distress syndrome
RM is a 66 y/o F s/p autologous PBSCT in the setting of MDS. She presents to the ICU day +20 with acute respiratory distress and was found to have DAH requiring intubation and subsequent paralysis. Which of the following would be a reason to consider avoiding use of steroids?

A. Advanced age
B. Use of paralytic
C. BMT associated DAH is a non-immune mediated process
D. Timing of DAH onset
Questions & Discussion