Non-Infectious Pulmonary Complications after Hematopoietic Stem Cell Transplantation

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Pulmonary Complications after Allogeneic HCT

Background

- Incidence = 40-60%
- A common cause of mortality before day 100.
- Accounts for about 30% of all immediate causes of death early after BMT
- Can be generally divided into:
  - Early (before day 100) vs. Late (after day 100)
  - Infectious (40%) vs. Non-Infectious (60%)

Soubani et al. Chest 1996
Early complications (usually < day +100)

- Non-infectious (or no pathogen identified)
  - Pulmonary edema/CHF
  - Idiopathic pneumonia syndrome (IPS)-
    - Diffuse alveolar hemorrhage (DAH)
    - Peri-engraftment respiratory distress syndrome (PERDS)
    - “Interstitial pneumonitis” without pathogen
  - Radiation/drug induced lung injury
  - Transfusion associated lung injury (TRALI)

- Infectious pneumonia
  - Bacterial
  - Viral (CMV, adenovirus, RSV, influenza, etc.)
  - Fungal/PCP
Late complications (after day +100)

- Non- infectious (associated w cGVHD)
  - Bronchiolitis Obliterans (B.O.)- Obstructive
  - Cryptogenic organizing pneumonia (COP/BOOP)
  - Idiopathic pneumonia syndrome (IPS)
  - Chest wall restriction (from sclerodermatous GVHD)

- Infectious (also more common w cGVHD)
  - Bacterial Bronchopneumonia (pneumococcus common)
  - Fungal
  - Viral
  - Nocardia
Pulm complications after SCT

Soubani et al. Chest 1996
**IPn/IPS question (form 2100)**

**Pulmonary Function**

410. Did the recipient develop interstitial pneumonitis (IPn or ARDS) / idiopathic pneumonia syndrome (IPS) after the start of the preparative regimen to the date of last contact (question 1)?

*Interstitial pneumonitis / idiopathic pneumonia syndrome is characterized on chest x-ray by hypoxia and diffuse interstitial infiltrates not caused by fluid overload.*

(Report bacterial and fungal pneumonia in Infection section (questions 379–407).)

1 □ yes  
2 □ no

411. Date of diagnosis of IPn / IPS: [ ] [ ] [ ]

Month Day Year

412. Were diagnostic tests done (other than radiographic studies)?

1 □ yes  
2 □ no

Diagnosis was evaluated by:

413. 1 □ yes  2 □ no  Bronchioalveolar lavage (BAL)
414. 1 □ yes  2 □ no  Transbronchial biopsy
415. 1 □ yes  2 □ no  Open / thorascopic (VATS) lung biopsy
416. 1 □ yes  2 □ no  Autopsy
417. 1 □ yes  2 □ no  Other test □□□□

418. Specify other test:

419. Was an organism isolated?

1 □ yes  
2 □ no / idiopathic

Etiology:

420. 1 □ yes  2 □ no  Adenovirus
421. 1 □ yes  2 □ no  Cytomegalovirus (CMV)
Confusing terminologies: Interstitial Pneumonitis (IPn) vs. Idiopathic Pneumonia Syndrome (IPS)

- Before 1993, the term “interstitial pneumonitis” (IPn) was used to describe:
  - Diffuse interstitial pneumonia on chest X-ray with associated hypoxia
  - Usually occurs early post BMT

- IPn can result from infectious or non-infectious causes.

- In 1993, the NIH/NHLBI formalized definition of IPS which includes ALL non-infectious lung injury that occurs early after SCT.

- IPn without infectious cause now falls under the umbrella definition of IPS.

- Use of term IPn is discouraged in HCT
Confusing terminologies: Interstitial Pneumonitis (IPn) vs. Idiopathic Pneumonia Syndrome (IPS)

- IPn and IPS are not the same!
- IPn = Pneumonia with “interstitial infiltrate” appearance on CXR, and/or a histopathologic appearance where the lung “interstitium” is infiltrated/thickened.
- IPn can result from infectious or non-infectious causes.
- IPS can only be used to denote an IPn without any infectious cause.

“interstitial pneumonia” pattern on CXR
Interstitial Pneumonitis (IPn)

- Normal lung histology
- Interstitial pneumonitis
Early Pulmonary complication

IPn
- Infectious
  - Viral
  - PCP
  - Atypical bacteria
- Non infectious Engraftment syndrome
- Idiopathic

Not IPn
- Non-Infectious DAH
- Infectious bacteria fungal

IPS
# Interstitial Pneumonitis (IPn) after AlloBMT

<table>
<thead>
<tr>
<th>Etiology:</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Viral</strong> ~ 50%</td>
</tr>
<tr>
<td>CMV</td>
</tr>
<tr>
<td>RSV</td>
</tr>
<tr>
<td>Adenovirus</td>
</tr>
<tr>
<td>Influenza/parainfluenza</td>
</tr>
<tr>
<td><strong>Pneumocystis (PCP)</strong> 5%</td>
</tr>
<tr>
<td><strong>Idiopathic (now categorized as IPS)</strong> ~ 50%</td>
</tr>
</tbody>
</table>

- **Onset:** Usually within first 100 days

- **Prevalence:** Allo > Syn > Auto SCT

Wingard et al. Medicine 67(3) 175-186. 1988
IPS accounts for about half of all IPn after BMT

<table>
<thead>
<tr>
<th>Institution (authors)</th>
<th>N</th>
<th>Incidence IP (%)</th>
<th>Idiopathic (%)</th>
<th>Mortality (%)</th>
<th>Risk Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>IBMTR 1977-1980 (Bortin et al. 1982)</td>
<td>176</td>
<td>36 (20%)</td>
<td>NR</td>
<td>58%</td>
<td>TBI dose MTX F-F D/R pair</td>
</tr>
<tr>
<td>IBMTR 1978-1983 (Weiner et al. 1986)</td>
<td>932</td>
<td>236 (35%)</td>
<td>50%</td>
<td>78%</td>
<td>Age &gt;21, PS &gt; 0 MTX, TBI dose GVHD, Time to Tx</td>
</tr>
<tr>
<td>J. Hopkins 1976-1985 (Wingard et al. 1988)</td>
<td>386</td>
<td>168 (43%)</td>
<td>50%</td>
<td>75%</td>
<td>GVHD, leukemia dx early time post BMT, MTX/Cy, CMV</td>
</tr>
<tr>
<td>Barcelona 1976-1990 (Granera et al. 1993)</td>
<td>311 (230 allo)</td>
<td>58 (19%)</td>
<td>40%</td>
<td>NR</td>
<td>Allogeneic donor, Acute GVHD CML Dx</td>
</tr>
</tbody>
</table>
Interstitial Pneumonitis (IPn) after BMT

N = 311 (230 allo, 73 auto, 8 syn)  

Granera et al. BMT 11:453, 1993
Idiopathic Pneumonia Syndrome

NIH Definition

- Evidence of widespread alveolar injury:
  - Multilobar infiltrates on CXR or CT
  - Symptoms/signs of pneumonia (cough, dyspnea, rales)
  - Evidence of abnormal pulmonary physiology
    - Increased A-a gradient
    - New restrictive PFT defect

- Absence of active lower respiratory tract infection:
  - Negative BAL for bacterial, viral, PCP, fungal pathogens
  - Confirmatory BAL, TBBx encouraged, but not required.

Idiopathic Pneumonia Syndrome (IPS)
Non-infectious, diffuse lung injury occurring early post BMT

IPS Historical Data

Onset of IPS (median): 15-40 days post transplant
Poor Outcome: 50 - 75% mortality
Histology: Interstitial pneumonitis (usually)
BAL fluid: elevated levels of TNFα noted
Pilot data: High response rates with TNFα binding agent: etanercept (Enbrel)*

Current trial: CTN 0403-Phase III study of etanercept + steroids vs Placebo + steroids

# Idiopathic Pneumonia Syndrome

<table>
<thead>
<tr>
<th>Institution (authors)</th>
<th>N</th>
<th>Incidence IPS (%)</th>
<th>Mortality (%)</th>
<th>Risk Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FHCRC 1988-1991</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Crawford et al. 1997)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allogeneic</td>
<td>956</td>
<td>7.6%</td>
<td>74%</td>
<td>Grade IV acute GVHD, Non-leukemia dx (Allo only)</td>
</tr>
<tr>
<td>Autologous</td>
<td>209</td>
<td>5.7%</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Michigan 1995-2000</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Cooke et al.)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allogeneic</td>
<td>425</td>
<td>7.5%</td>
<td>94%</td>
<td>NR</td>
</tr>
</tbody>
</table>
**IPn/IPS question (form 2100)**

**Pulmonary Function**

410. Did the recipient develop interstitial pneumonitis (IPn or ARDS) / idiopathic pneumonia syndrome (IPS) after the start of the preparative regimen to the date of last contact (question 1)?

*Interstitial pneumonitis / idiopathic pneumonia syndrome is characterized on chest x-ray by hypoxia and diffuse interstitial infiltrates not caused by fluid overload.*

(Rest of the text not relevant to the question)

411. Date of diagnosis of IPn / IPS:

- ❑ yes
- ❑ no

412. Were diagnostic tests done (other than radiographic studies)?

- ❑ yes
- ❑ no

Diagnosis was evaluated by:

- ❑ yes 2 no Bronchoalveolar lavage (BAL)
- ❑ yes 2 no Transbronchial biopsy
- ❑ yes 2 no Open / thorascopic (VATS) lung biopsy
- ❑ yes 2 no Autopsy
- ❑ yes 2 no Other test

418. Specify other test: __________________

419. Was an organism isolated?

- ❑ yes
- ❑ no

Etiology:

- ❑ yes 2 no Adenovirus
- ❑ yes 2 no Cytomegalovirus (CMV)

This is the definition of IPn, not IPS

“no” here defines IPS
Non-infectious and “non-IPn” pulmonary complication early after HCT:
Diffuse Alveolar Hemorrhage (DAH)

DAH - subset of IPS that occurs early post HCT, around engraftment.
Associated with hemorrhage in small airways and alveoli

Bilateral patchy alveolar opacities in a patient with DAH
# Diffuse Alveolar Hemorrhage (DAH)

- **Definition:**
  - Clinical syndrome early post HSCT
  - Progressive dyspnea
  - Hypoxia, hypoxemia
  - Diffuse patchy consolidation on chest X-ray
  - Increasing bloody returns on successive BAL
  - Absence of identifiable infectious pathogen

- **Clinical Findings**
  - Dyspnea
  - Tachypnea
  - Non-productive cough (hemoptysis rare)
  - Fever
Diffuse Alveolar Hemorrhage (DAH)

Background

- Originally described in autologous BMT, but more common after allogeneic HSCT.

- Incidence
  - 1-5% after autologous HSCT
  - 5-15% after myeloablative allogeneic HSCT

- Characteristic time of onset:
  - 2-3 weeks after transplant
  - Around time of engraftment

- Treatment - steroids, high dose steroids
- Mortality rate 70-80%

Diffuse Alveolar Hemorrhage (DAH)

- Diagnosis of DAH requires bronchoscopy:
  - Bronchial mucosa erythematous and edematous
  - No mucosal ulceration, no clear source of bleeding
  - Sequential instillation of saline results in BAL fluid that is progressively bloodier with each aliquot.
## DAH Following Myeloablative HCT

<table>
<thead>
<tr>
<th>Institution</th>
<th>Number patients</th>
<th>Number with DAH (%)</th>
<th>Acute Mortality (%)</th>
<th>Overall survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nebraska 1983-1987 (Robbins et al. 1989)</td>
<td>141</td>
<td>29 (20.5)</td>
<td>79%</td>
<td>10% (2 yr)</td>
</tr>
<tr>
<td>Auto</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stanford 1987-1990 (Chao et al. 1991)</td>
<td>77</td>
<td>4 (5.0)</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>Auto</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nebraska 1985-1990 (Metcalf et al. 1994)</td>
<td>494</td>
<td>65 (10.4)</td>
<td>75%</td>
<td></td>
</tr>
<tr>
<td>Auto</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allo</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Minnesota 1991-1997 (Lewis et al. 2000)</td>
<td>426</td>
<td>4 (0.9)</td>
<td>74%</td>
<td>26% (1.5 yr)</td>
</tr>
<tr>
<td>Auto</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allo</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Allo</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DFCI/BWH 1997-1998 (Ho et al. 2001)</td>
<td>341</td>
<td>25 (7.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Auto</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allo</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>140</td>
<td>1 (0.7)</td>
<td>70%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>199</td>
<td>23 (11.5)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Late Non-infectious Pulmonary complication

Obstructive

Bronchiolitis Obliterans Syndrome (B.O.S)

Restrictive

COP/BOOP
- ? Late IPS
- ?late drug tox

Chest wall restriction
Bronchiolitis Obliterans (B.O.)

- Term utilized as both a morphologic descriptor and clinicopathologic syndrome.

- BO describes an intraluminal polypoid plug of granulation tissue found within terminal bronchioles.

- Non-specific pathology finding

- Associated with cGVHD in HSCT

- Associated with rejection after lung transplantation

- The clinical condition associated with B.O. on path should be called “bronchiolitis obliterans syndrome” (BOS).
## Bronchiolitis Obliterans (BO/BOS)

### Clinical presentation and diagnosis:

- Nonspecific injury affecting mainly small airways (asthma like syndrome)

- Patients present with gradual onset of dyspnea, dry cough, wheezing. Fever is distinctly uncommon.

- Onset: >3 months to 10 yrs post HCT, median 1 year

- Chest X-ray and CT scans usually clear (lung parenchyma spared)

- Diagnosis- Based mainly on pulmonary function testing (PFTs) showing airway obstruction
  - FEV1 decline >20% from baseline
  - FEV/FVC ratio <0.7

- BAL/lung biopsy useful to rule out infection, **not** required for diagnosis.
Bronchiolitis Obliterans (BO/BOS)

Incidence

- Due to lack of clearly defined diagnostic criteria, BO/BOS incidence after alloHCT varies widely in literature!

- Reported incidence: 1.7% (CIBMTR) to 26%.

- BO/BOS is likely under diagnosed and reported unless routine PFT screening is performed post HCT.
## Bronchiolitis Obliterans (BO/BOS)

### Risk Factors

- **Strong association with chronic GVHD**
- **Other reported risk factors:**
  - Methotrexate GVHD prophylaxis
  - Low serum IgG levels
  - Low FEV/FVC before transplant
  - Respiratory viral infection within first 100 days
  - Prior interstitial pneumonia (IPn)
  - Prior acute GVHD
  - Busulfan based myeloablative conditioning
  - PBSC stem cell source
  - Female donor male recipient
  - Longer duration from leukemia dx to transplant

Bronchiolitis Obliterans (BO/BOS)

**Treatment**
- Prolonged steroids (Prednisone)
- Immune suppressives: Cyclosporine or imuran
- Prolonged macrolide antibiotic (azithromycin) for its "anti-inflammatory" property
- Leukotriene inhibitors (Monteleukast/Singulair®)
- Imatinib (Gleevec®)
- Extracorporeal photophoresis
- Lung transplantation

**Prognosis**
- Prognosis despite treatment remains poor:
  - Only 8-20% have improvement in PFTs
  - 3-year mortality 65% (Clark et al. 1989)
Late Non-infectious Pulmonary complication

Obstructive
  - Bronchiolitis Obliterans Syndrome (B.O.S)

Restrictive
  - COP/BOOP
    - ? Late IPS
    - ? Late drug tox
  - Chest wall restriction
Bronchiolitis Obliterans with organizing pneumonia (BOOP)

- BOOP is distinct from BO/BOS.
- Involves mainly alveoli ducts and alveoli (air sacs).
- Pathology: Granulation tissue found within alveolar ducts and air sacs.
- Outside of HCT, BOOP can be seen as a result of infection, drug or radiation toxicity, rheumatologic disease, organ transplantation.
- Idiopathic BOOP also known as cryptogenic organizing pneumonia (COP)

From: Eppler GR. Arch Int. Med. 161 (2). 2001
BOOP/COP

Clinical presentation and diagnosis

- Onset 1-12 months post HCT, median about 4 months.
- Presents more like "pneumonia": fever, dry cough, and dyspnea.
- CXR/CT: Diffuse "fluffy" infiltrates, ground glass opacity, nodular opacities.
- PFT show a restrictive pattern, with decreased DLCO and TLC.
- Bronchoscopy/BAL important for ruling out infection.
- Lung biopsy demonstrating organizing pneumonia is the gold standard for establishing the diagnosis of BOOP/COP.
BOOP/COP

Risk factors:
- Acute GVHD (skin)
- Chronic GVHD (mouth, gut)
- Unrelated donor HCT

Treatment and Prognosis:
- Prognosis more favorable for BOOP/COP compared to BO, with mortality around 20%.
- About 80% of patients with BOOP/COP after HCT will respond to treatment.
- Primary treatment includes 1-3 months of prednisone (approx 1mg/kg), with slow taper to avoid relapse.

Patriarca et al. BMT 33: 751-758. 2004
## Summary: BO/BOS vs. BOOP/COP

<table>
<thead>
<tr>
<th></th>
<th>BOS</th>
<th>BOOP</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Symptom</strong></td>
<td>Progressive Dyspnea</td>
<td>Fever</td>
</tr>
<tr>
<td></td>
<td>Non-productive cough</td>
<td>Non-productive cough</td>
</tr>
<tr>
<td></td>
<td>Wheezing</td>
<td>Dyspnea</td>
</tr>
<tr>
<td><strong>Physical exam</strong></td>
<td>Wheezing</td>
<td>Rales</td>
</tr>
<tr>
<td><strong>Lab data</strong></td>
<td>Non-specific</td>
<td>Elevated CRP</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Increased Neutrophil</td>
</tr>
<tr>
<td><strong>PFT</strong></td>
<td>Obstructive lung disease</td>
<td>Restrictive lung disease</td>
</tr>
<tr>
<td><strong>FEV1/FVC</strong></td>
<td>Decreased</td>
<td>Normal</td>
</tr>
<tr>
<td><strong>TLC</strong></td>
<td>Normal</td>
<td>Decreased</td>
</tr>
<tr>
<td><strong>DLCO</strong></td>
<td>Decreased</td>
<td>Decreased</td>
</tr>
<tr>
<td><strong>Radiology/CT scan</strong></td>
<td>Air trapping (expiratory phase)</td>
<td>Consolidation</td>
</tr>
<tr>
<td></td>
<td>Mosaic perfusion</td>
<td>Ground glass opacitiy</td>
</tr>
<tr>
<td></td>
<td>Bronchiectasis</td>
<td>Nodular opaciites</td>
</tr>
<tr>
<td></td>
<td>Bronchial wall thickening</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Centrilobar nodules</td>
<td></td>
</tr>
</tbody>
</table>

Adapted from Yoshihara et al. BBMT 2007
Non-infectious pulmonary complication question (form 2100)

433. Did the recipient develop non-infectious pulmonary abnormalities (other than IPn / IPS / ARDS) after the start of the preparative regimen to the date of last contact (question 1)?
1  yes
2  no

434. Did the recipient develop bronchiolitis obliterans after the start of the preparative regimen to the date of last contact (question 1)?
1  yes
2  no

435. Date of diagnosis:
   Month  Day  Year

436. Were diagnostic tests done?
1  yes
2  no

   Diagnosis was evaluated by:
   437. 1  yes  2  no Bronchoalveolar lavage (BAL)
   438. 1  yes  2  no Transbronchial biopsy
   439. 1  yes  2  no Open / thorascopic (VATS) lung biopsy
   440. 1  yes  2  no Autopsy
   441. 1  yes  2  no Other

443. Did the recipient develop pulmonary hemorrhage?
1  yes
2  no

444. Date of diagnosis:
   Month  Day  Year

445. Were diagnostic tests done?
1  yes
2  no

   Diagnosis was evaluated by:
   446. 1  yes  2  no Bronchoalveolar lavage (BAL)
   447. 1  yes  2  no Transbronchial biopsy
   448. 1  yes  2  no Open / thorascopic (VATS) lung biopsy
   449. 1  yes  2  no Autopsy
   450. 1  yes  2  no Other

“yes” for BO/BOS
BO/BOS uncommon before day 100!

“yes” for DAH (not for hemorrhage from infection)
Non-infectious pulmonary complication question (form 2100)

452. Did the recipient develop cryptogenic organizing pneumonia (COP)?
1 □ yes 2 □ no

453. Date of diagnosis:
Month  Day  Year

454. Were diagnostic tests done?
1 □ yes 2 □ no

Diagnosis was evaluated by:
455. 1 □ yes 2 □ no Bronchoalveolar lavage (BAL)
456. 1 □ yes 2 □ no Transbronchial biopsy
457. 1 □ yes 2 □ no Open / thorascopic (VATS) lung biopsy
458. 1 □ yes 2 □ no Autopsy
459. 1 □ yes 2 □ no Other → 460. Specify:

“yes” for BOOP

BOOP is the same as COP!
**Summary: Early Pulmonary Complications**

- *Interstitial pneumonitis (IPn)*- old terminology referring to a radiographic and histologic pattern of pneumonia
  - IPn can be infectious or non-infectious in etiology
  - Non-infectious (idiopathic) IPn is included under the definition of idiopathic pneumonia syndrome

- *Idiopathic pneumonia syndrome (IPS)* encompasses all non-infectious pneumonia in the first 120 days of HCT

- *Diffuse alveolar hemorrhage (DAH)* is another clinical entity included under the umbrella definition of IPS.
  - DAH occurs very early post HCT, around neutrophil engraftment
  - DAH diagnosis requires presence of progressive bloody lavages on BAL, and absence of infection
Summary: Late Pulmonary Complications

- Usually associated with chronic GVHD
- Can be divided in “Obstructive” vs. “Restrictive” lung disease by PFT
  - Obstructive lung disease = BO/BOS
  - Restrictive lung disease = BOOP/COP
- BO/BOS and BOOP/COP are distinct diseases:
  - BO/BOS – insidious onset
    - Affects terminal small airways (asthma like)
    - CXR/CT usually clear
    - Usually unresponsive to treatment, poor prognosis
  - BOOP/COP – abrupt onset
    - Affects predominantly air sacs (alveoli)
    - Resembles pneumonia – fever, infiltrates on X-ray, CT
    - Very responsive to steroids, good prognosis