Lung Injury after HCT

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Background

- **HCT an important therapeutic modality for malignant and non-malignant diseases**
- **Pulmonary Toxicity common**
  - **25-55% of all recipients**
  - **Substantial contribution to treatment-related mortality**

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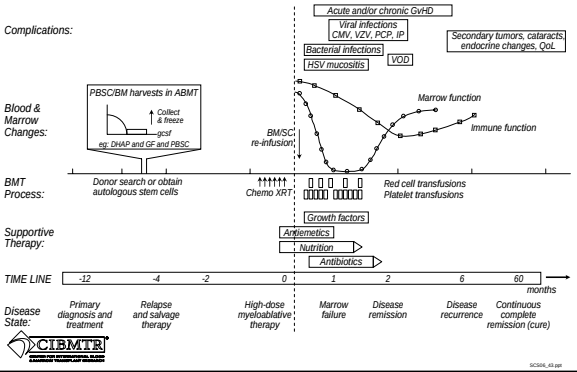
Timeline of Transplant



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Infectious Lung Injury

- Viral
  - CMV
  - Community Respiratory Viruses
- Bacterial
  - Pneumococcus, atypical organisms, PCP
- Fungal

Non-infectious Lung Injury

- 50% of post HCT lung injury is NOT infectious
- Acute
  - Idiopathic pneumonia syndrome
- Sub-acute
  - Bronchiolitis obliterans
  - Restrictive Lung disease

NIH Definition of IPS

- Widespread alveolar injury after HCT in absence of active lower respiratory infection or cardiogenic causes
- Clinical syndrome
  - Variable histology
  - Several Etiologies

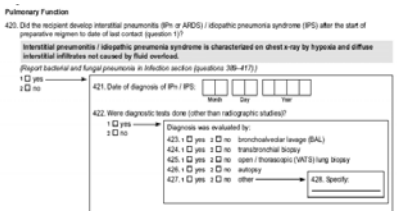
IPS

- Widespread lung injury
  - Multilobar infiltrates (CT or CXR)
  - Signs/sx of pneumonia
    - Cough, dyspnea
  - Abnormal pulmonary physiology
    - Increased A-a gradient
    - Restrictive Lung findings

Absence of Lower Respiratory Tract infection

- BAL negative for bacterial pathogen or no response to broad spectrum antibiotics
- BAL negative for non-bacterial pathogens
- Transbronchial lung biopsies
- Confirm testing negative for infection 2-14 days later

Reporting IPS


Pulmonary Function

420. Did the recipient develop interstitial pneumonitis (IPn or ARDS) / idiopathic pneumonia syndrome (IPS) after the start of preparative regimen to 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 389-417).)

1 ☐ yes → 421. Date of diagnosis of IPn / IPS: Month Day Year

2 ☐ no

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

1 ☐ yes → Diagnosis was evaluated by:

423. 1 ☐ yes 2 ☐ no bronchoalveolar lavage (BAL)

424. 1 ☐ yes 2 ☐ no transbronchial biopsy

425. 1 ☐ yes 2 ☐ no open / thoracoscopic (VATS) lung biopsy

426. 1 ☐ yes 2 ☐ no autopsy

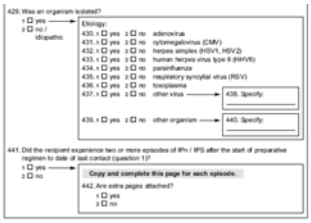
427. 1 ☐ yes 2 ☐ no other → 428. Specify:

2 ☐ no

Histopathology

- Diffuse alveolar damage
- Bronchiolitis obliterans organizing pneumonia
- Interstitial pneumonitis

Reporting IPS II



IPS II

- Incidence 3-15% (25%) first 4 months
- Median onset 6-7 wks (2-12)
- Mortality 60-80%
  - 95% if ventilator required
- Median time to death from diagnosis 13 days

How Bad Does it Get?

473. Did the recipient receive endotracheal intubation or mechanical ventilation post-HSCT?
1 ☐ yes
2 ☐ no

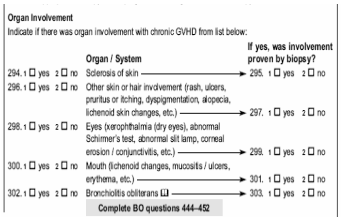
Risk factors for IPS

- TBI
- aGVHD
- Older recipient
- Use of MTX
- BCNU
- Malignancy other than leukemia
- Poor Perf score at HCT
- Increased HLA disparity
- Allogeneic (vs autologous)
- Ablative conditioning

Possible Causes of IPS

- Direct toxicity of chemo-radiotherapy
- Occult pulmonary infections
- Inflammatory cytokines
  - TNF alpha, Lipopolysaccharide
- Donor derived cellular effectors
  - Alloreactive T cells

IPS in GVHD



Organ Involvement

Indicate if there was organ involvement with chronic GVHD from list below:

	Organ / System	If yes, was involvement proven by biopsy?
294. 1 ☐ yes 2 ☐ no	Sclerosis of skin →	295. 1 ☐ yes 2 ☐ no
296. 1 ☐ yes 2 ☐ no	Other skin or hair involvement (rash, ulcers, pruritus or itching, dyspigmentation, alopecia, lichenoid skin changes, etc.) →	297. 1 ☐ yes 2 ☐ no
298. 1 ☐ yes 2 ☐ no	Eyes (xerophthalmia (dry eyes), abnormal Schirmer's test, abnormal slit lamp, corneal erosion / conjunctivitis, etc.) →	299. 1 ☐ yes 2 ☐ no
300. 1 ☐ yes 2 ☐ no	Mouth (lichenoid changes, mucositis / ulcers, erythema, etc.) →	301. 1 ☐ yes 2 ☐ no
302. 1 ☐ yes 2 ☐ no	Bronchiolitis obliterans ☐ →	303. 1 ☐ yes 2 ☐ no

Complete BO questions 444–452

Role of TNF alpha

- TNF alpha
  - Effector cytokine for GVHD
  - Patients with higher TNF with preparative regimen higher risk of GVHD
  - May play early role in gut GVHD
- Causal role in IPS after alloHCT in mouse experimental models

General Treatment of IPS

- Support
  - Oxygen/ventilation
  - Broad spectrum antibiotics
  - Diuretics, CVVH(D)
- Immune suppression
  - Corticosteroids
  - Cytokine inhibitors
  - KGF
  - Chemokine receptor agonists

New treatment in IPS

- Neutralization of TNF alpha can alter lung injury progression in mice
- Etanercept has soluble TNF receptors bound to IgG
- Early investigational treatment in humans promising

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Etanercept at U Mich

- 15 patients U Mich and DFCI
- 56 day survival
  - Etanercept+ Steroids – 60%
  - Steroids alone – 26%
- Median time to response 7d

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Treatment of Idiopathic Pneumonia

- CTN 0403 Therapy for Idiopathic Pneumonia Syndrome
  - Baseline 50-70% mortality rates
  - Investigate role of Etanercept to treat IPS in Phase III RCT
  - Is Etanercept + Steroids more effective than steroids alone?
    - 8 doses Etanercept over 4 weeks

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CTN 0403

- Primary endpoint will be response to treatment
  - 28 days following treatment
- Laboratory correlates to evaluate biology of IPS using serum and BAL fluid
  - TNF, LPS activation system

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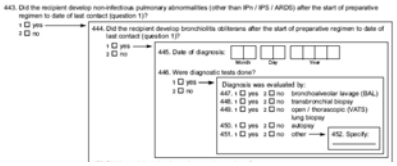
Other Lung Injury



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Bronchiolitis Obliterans Syndrome

- Cough, dyspnea, wheezing
- Onset 3-24 mos
- PFTs – obstruction (low FEV1)
- Radiographic – hyperinflation
  - CT with bronchiectasis, ground glass
- Pathology – bronchiolar inflammation with luminal obliteration

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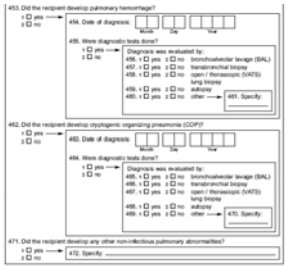
Other Lung Injury



Diffuse Alveolar Hemorrhage

- Dyspnea, cough, rare hemoptysis
- Onset within first 100 days
- Radiographic: diffuse infiltrates, central appearance initially
- Diagnostic: BAL with progressively bloodier fluid
- Path: diffuse alveolar damage with blood

BOOP / COP

- Bronchiolitis obliterans organizing pneumonia (cryptogenic organizing pneumonia)
- Radiographic: Patchy airspace disease, ground glass or nodular opacities
- Path: peribronchiolar infiltration and fibrosis

COOP vs. BOS

- Restrictive lung disease with low lung volumes
- Exam like pneumonia
- Good response to steroids
- Obstructive pattern with air-trapping, hyperinflation
- Exam like COPD – quiet, may have wheezes
- Poor response to steroids

Conclusions

- Lungs frequently target of post-HCT complications
- Infectious and non-infectious
- Frequently fatal
- Newer agents may substantially improve outcomes