How the Experts Treat Hematologic Malignancies
Las Vegas, NV
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Disclosures

No disclosures
Objectives

• Describe post transplant issues and give nursing care considerations related to:
  – Hepatic complications
  – Renal complications
  – Neurologic complications
  – Genitourinary complications
  – Endocrine complications
  – Cardiac complications
  – Pulmonary complications

Note: the primary reference sources for this course are
Hepatorenal complications

- Hepatic
  - There are two general patterns of hepatic injury
    - Acute inflammation / hepatocyte injury (AST and ALT elevated)
    - Cholestatic injury (alkaline phosphatase and bilirubin* elevated)
  
  - *Note that for hepatic injury, we are looking for increased total and direct bilirubin, not just total bilirubin alone
Hepatorenal complications

- Hepatic
  - More common after Allo HCT
    - Can affect up to 80% of patients
    - 5 -15% treatment related mortality
  - Pretransplant factors
    - Pre-existing liver disease (e.g. Hepatitis B or C) (Note: people with cirrhosis of the liver are generally not candidates for HCT)
    - Liver metastasis
    - Infection or sepsis during conditioning regimen
    - Intensive conditioning regimen, previous chemotherapy, prior transplant, prior radiation to the liver
      - Busulfan-based regimens are more likely to cause sinusoidal obstructive syndrome (SOS), especially in conjunction with sirolimus as GVHD prophylaxis
    - Mismatched or unrelated donor
Veno-occlusive Disease: Clinical Manifestations
(More currently called Hepatic Sinusoidal Obstructive Syndrome [SOS])

- Right upper quadrant (RUQ) pain
- Weight gain
- Ascites
- Edema
- Hepatomegaly
- Jaundice
Sinusoidal Obstructive Syndrome: Diagnosis

SOS is a clinical diagnosis

- No single lab or radiology test which makes a diagnosis
- Clinical criteria (weight gain, ascites, jaundice, RUQ pain)
- Ultrasound findings can support the diagnosis by demonstrating ascites and abnormal flow in the portal vein (especially if flow is reversed)
- Liver biopsy can be performed to help with the diagnosis but is rarely done due to the potential morbidity
SOS: Treatment

Treatment is primarily supportive

- Mild and moderate cases may resolve spontaneously
- Prophylaxis is often given preemptively in allogeneic HCT
  - Ursodiol PO BID
  - Low-dose heparin continuous infusion
    - Neither has strong supportive evidence, but fairly low risk
- Nursing considerations: strict I/Os, monitor fluid status, weights
- Severe SOS can be treated with defibrotide
  - Associated with significant bleeding risks
Severe SOS leads to Hepatorenal Syndrome

**Symptoms**
- Relative hypotension
- ↓ flow from hepatic vessels
- Renal vasoconstriction
- Urinary sodium retention
- Edema/ascites
- Reduced glomerular filtration rate (GFR)
- ↓ urine output

**Treatment**
- Restriction
  - Protein
  - Fluid
  - Sodium
- Renal dose dopamine
- Diuretics
- Hemofiltration
  - Continuous Arteriovenous
    - Hemofiltration with Dialysis (CAVHD)
  - Continuous Renal Replacement Therapy (CRRT)

* If SOS progresses to this point, the mortality rate is very high
Drug-Induced Liver Injury

- Conditioning regimen (busulfan, TBI-based regimens)
- Immunosuppressants – sirolimus, especially in conjunction with busulfan-based myeloablative regimens
- Antimicrobial agents – especially the azole medications
- Hyperalimentation (HAL) – Prolonged TPN can result in liver dysfunction
Graft-versus-host disease

- The liver is a common site affected by GVHD
- Although not a hard and fast rule, hepatic GVHD tends to manifest itself as a rise in bilirubin and alkaline phosphatase (cholestatic picture) more than AST/ALT
- Treatment follows GVHD paradigm
Renal Complications: Pathophysiology

- Epithelial cell damage
  - Nephrotoxic injury
  - Ischemic injury
- Compromised renal blood flow
- Impaired ability to remove fluid, electrolytes and metabolic waste
- Increased
  - Weight
  - Blood pressure
  - Serum creatinine & BUN
Renal Complications During HCT

- General acute injury in HCT, since patients are required to have adequate renal function to be eligible for HCT
  - May be chronic
- Multiple types of injury possible
  - Sepsis-induced renal injury (often due to hypotension and resulting poor renal perfusion)
  - Tumor lysis syndrome – aggressive tumors and high burden of disease (rapid LDH and/or uric acid release damages kidneys)
  - Thrombotic microangiopathy (TTP or Hemolytic uremic syndrome – direct damage to the glomerular capillaries)
  - Radiation nephritis – direct insult to kidneys
  - Syndrome of inappropriate antidiuretic hormone (SIADH)
Renal Complications: Pre-renal

- Most common
- Poor perfusion
- Etiology
  - Hypovolemia
  - Impaired circulation
  - Vascular constriction
Pre-renal Complications: Hypovolemia

- Dehydration
  - Fever (increased insensible fluid losses)
  - Excessive diuresis
  - Gastrointestinal losses (i.e. diarrhea)
  - Hemorrhage
- Capillary leak syndrome (CLS)
- Hepatorenal syndrome
Capillary Leak Syndrome: Etiology

Any critically and acutely ill patient is at risk

- Aspiration
- Pneumonitis
- Radiation therapy
- Poor perfusion to the lung
- Sepsis – Cytokine Release Syndrome
- Disseminated intravascular coagulopathy (DIC)
- Chemotherapy
- Immunotherapy
  - CAR T-cell clinical trials
  - IL-2
Post-renal Complications: Hemorrhagic Cystitis

- **Etiology**
  - Chemotherapy (cyclophosphamide)
  - Viral infections (adenovirus or BK virus)
  - Radiation

- **Symptoms**
  - Dysuria
  - Urgency
  - Bladder spasms
  - Hematuria (gross blood and clots)

- **Diagnosis**
  - Ultrasound
  - Urology consult
Hemorrhagic Cystitis – medical / nursing management and treatment

• Prevention
  – Aggressive IV hydration / strict intake and output
  – Mesna® prophylaxis

• Treatment
  – Continuous bladder irrigation – 500ml to 2 L/hr
  – Maintain platelet count
  – Cystoscopy with cauterization if there is a visible lesion
  – Urine culture and treatment of underlying infection
  – Aluminum irrigation of bladder for persistent bleeding
  – Phenazopyridine for dysuria (no “magic bullet” for bladder spasm pain)
  – Pain management
Intra-Renal Complications: Hemolytic Uremic Syndrome

Clinical features
- Thrombocytopenia
- Hematuria
- Hypertension
- Renal failure
- Microangiopathic hemolytic anemia – increase schistocytes and nucleated RBCs in the peripheral blood
- Diffuse endothelial damage

Clinical manifestations
- Bruising, bleeding, petechiae, CNS changes, fatigue, pallor, fever, ↑ LDH
Radiation Nephritis

• Late syndrome
  – 3 to 13 months post-HCT

• Clinical Features
  – ↑ BUN & creatinine
  – Anemia & hypertension

• Risk factors
  – Multi-agent conditioning regimens
  – Total body irradiation
Renal Complications: Nursing Assessment

- Weight
- Strict I&O
- Estimate insensible loss
  - Adult – approximately 800 mL / day (= heat loss of about 480 kCal / day)
  - Increases with fever, rigors
- Postural blood pressure / orthostatic measurements
- Heart rate
- Abdominal girth
- Lung exam
- Peripheral edema
- Mental status
- Monitor labs
Neurologic Complications

- Delirium
  - Conditioning regimen, drug therapy, metabolic disturbances
  - Age
- Seizures
  - Associated with busulfan – prophylaxis given
  - May occur with BCNU
  - Rarely may occur with DMSO
- Metabolic encephalopathy
  - Metabolic acidosis
  - Renal or hepatic failure
  - Sepsis
  - Hypoxemia
  - Electrolyte disturbances
Neurologic Complications

- Leukoencephalopathy
  - Syndrome of unclear etiology which results in irreversible damage in the brain’s white matter
    - Associated with ALL, cranial radiotherapy, and intrathecal methotrexate
- PML – Progressive Multifocal Leukoencephalopathy
  - Allo patients who experienced prolonged immunosuppression
  - Rare and extremely high mortality rate
  - Confusion, visual and speech disturbances, imbalance
- Posterior Reversible Encephalopathy Syndrome (PRES)
  - Calcineurin inhibitor toxicity (toxic levels of CSA or tacrolimus)
  - Reversible by dose adjustment
  - Symptoms of visual disturbances, altered mental status, hypertension, headache, seizures
Neurologic Complications

• Infectious sources causing CNS infection
  – Viral
  – Bacterial (less common)
  – Fungus
  – Present with headache, nuchal rigidity, seizures, mental status changes, delirium and depressed sensorium

• Cerebrovascular
  – Post-transplant hypercoaguable state
    • Decrease in protein C and antithrombin
    • Increase in fibrinogen
  – Prolonged thrombocytopenia
  – Risk of
    • Intracranial hemorrhage, subdural hematoma, and ischemic stroke
Genitourinary complications

- Vaginal sicca
- Vaginal atrophy, stenosis or inflammation
  - If cGVHD related, may respond to topical corticosteroid, cyclosporine or tacrolimus
  - Use of vaginal lubricants and dilators
  - Low-dose topical estrogen (vaginal atrophy)
- Hemorrhagic cystitis
- Nephrotic syndrome may develop (cGVHD or renal insult)
  - Edema
  - Proteinuria
Endocrine complications

• Hyperglycemia
  – Steroid-induced hyperglycemia
  – Literature suggests tight control of serum glucose during transplant course may improve outcomes

• Syndrome of Inappropriate Anti-Diuretic Hormone
  – Cyclophosphamide common culprit (although many drugs can cause SIADH)
  – Release of antidiuretic hormone
    • Fluid retention
      – Hydration
      – Diuretics
      – Monitor weight, intake and output, lung sounds

• Hypothyroidism – usually resulting from radiation to the mediastinum and total body irradiation
Post Transplant Complications: Cardiac

- Incidence 25%
- Mortality rare
- Pre-transplant screening
  - Echocardiogram – Ejection Fraction ≥ 50%
  - EKG baseline
- Causes
  - Conditioning regimen and prior treatments:
    - Anthracyclines
      - Cumulative doses ≥ 400 mg/m² (Doxorubicin, Daunorubicin)
      - Early post-HCT damage can cause necrosis and fibrosis and can be irreversible
    - Cyclophosphamide
    - Mediastinal radiation
    - Total body irradiation
    - Pre-existing cardiac disease
    - Sepsis / inflammation
Cardiotoxic Side Effects

• Cardiac arrhythmia is the most common cardiotoxic side effect of HSCT, followed by congestive heart failure, pericarditis, pericardial effusion, and pulmonary edema (Deaver, 2008; Soubani, 2006)

• Calcineurin inhibitors (Tacrolimus, Sirolimus) often associated with hypertension
  – May be concurrent hyperkalemia
Pericardial Effusion and Tamponade

• Cyclophosphamide toxicity, viral or bacterial infection, or renal failure may contribute to the development of pericardial effusion and tamponade

• Aggressive treatment with pericardiectomy or pericardiocentesis is indicated in the instance of hemodynamic impairment (Soubani, 2006)

• Hemodynamic impairment generally occurs when pericardial effusion progresses to pericardial tamponade
Pericarditis - Symptoms

Sentinel symptom is retrosternal pain exacerbated upon inhalation or assuming a supine position

- Relief from pain often is obtained when the patient sits up and leans forward
- This also is the position in which the characteristic pericardial friction rub is best auscultated along the left sternal boarder

Hallmark signs of pericardial tamponade include:

- Pulsus paradoxus **Definition:** On inspiration, a drop in systemic arterial pressure *greater* than 10mmHg
- Hypotension
- Distant heart sounds
- Tachypnea
- Dyspnea
- Elevated central venous pressure (this is considered an oncologic emergency) (Burgunder, 2007)
Timeline for pulmonary complications post HCT

- Upper airway complications
- Diffuse alveolar hemorrhage
- Pulmonary edema
- Pleural effusion
- Radiation pneumonitis
- Veno-occlusive disease
- Acute GVHD
- Idiopathic pneumonia syndrome
- Pulmonary cytolytic thrombi
- Secondary malignancies
- Chronic GVHD
- Bronchiolitis obliters
- Radiation fibrosis

First 100 days

Months after BMT

- Up to 14 years
- Up to 2 years
Assessment of Pulmonary Complications

- Plain chest x-ray remains the mainstay for assessing patients for pulmonary complications
- CT scan may be ordered for more definitive diagnosis when chest x-ray becomes abnormal
- Pulmonary Function Test (PFT)
- Bronchoalveolar lavage (BAL) – diagnosis of pulmonary infections
- Lung biopsy
Pulmonary Complications

- **Pleural effusions**
  - Fluid overload, CHF, dyspnea, tachypnea, cough, weight gain, bilateral rales, hypoxemia
  - Diuretics, oxygen support, thoracentesis, if needed

- **Pulmonary embolism**

- **Idiopathic Pneumonia Syndrome**
  - Diffuse interstitial pneumonitis and alveolar injury
  - Hypoxemia, dyspnea, non-productive cough, non-specific infiltrates on x-ray
  - Supportive treatment
# Diffuse Alveolar Hemorrhage

<table>
<thead>
<tr>
<th>Signs</th>
<th>Sudden onset dyspnea, cough, hemoptysis rare</th>
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</thead>
<tbody>
<tr>
<td>Symptoms</td>
<td>Crackles, progressive hypoxemia, fever</td>
</tr>
<tr>
<td>X ray</td>
<td>Diffuse consolidation</td>
</tr>
<tr>
<td>BAL</td>
<td>Progressively bloody return</td>
</tr>
<tr>
<td>Cytology</td>
<td>Hemosiderin laden macrophages</td>
</tr>
<tr>
<td>Treatment</td>
<td>Platelet transfusion support, oxygen support, high dose corticosteroids</td>
</tr>
</tbody>
</table>
Figure 1. Schematic diagram of the time of occurrence of IPS, BOOP, and BOS.

Satoshi Yoshihara, Gregory Yanik, Kenneth R. Cooke, Shin Mineishi

Bronchiolitis Obliterans Syndrome (BOS), Bronchiolitis Obliterans Organizing Pneumonia (BOOP), and Other Late-Onset Noninfectious Pulmonary Complications following Allogeneic Hematopoietic Stem Cell Transplantation

http://dx.doi.org/10.1016/j.bbmt.2007.05.001
Bronchiolitis Obliterans Syndrome (BOS)

- Obstructive airway disease from granulation tissue plugs in the lumens of the small airways
- Onset – three months to two years post HCT
- Clinical course may be mild with slow deterioration
- Symptoms:
  - Wheezing
  - Non-productive cough
  - DOE
- Associated with chronic GVHD
Bronchiolitis Obliterans Syndrome (BOS)

- **Risk Factors:**
  - Use of CSA with prednisone for GVHD prophylaxis
  - Low serum IgG
  - TBI preparative regimens

- **Diagnosis:**
  - High resolution CT scan of chest – represents pulmonary air trapping and poorly defined lung margins
  - Pulmonary function test

- **Treatment:**
  - High dose steroids – and taper
Bronchiolitis Obliterans Syndrome (BOS)

Rare in transplant population: 5-30%
Associated risk factors:
  - Methotrexate
  - CMV infection
  - Busulfan
  - Carmustine
Can occur at any time during transplant course
Treatment:
  - Steroids
  - Supportive care

Figure 3. CT scan of BOS. Mosaic pattern of air trapping is clearly shown in expiratory phase.

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Bronchiolitis Obliterans Organizing Pneumonitis

- Restrictive disorder associated with chronic GVHD
  - Insidious onset with formation of fibromyxoid connective tissue plugs
  - Scarring and obstruction
- Progressive flu-like symptoms: nonproductive cough, decreased exercise tolerance, dyspnea
- Treatment: immunosuppressive agents
- Poor prognosis
## Comparison of Clinical Presentations of BOS and BOOP

<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 (usual mild)</td>
</tr>
<tr>
<td><strong>Physical examination</strong></td>
<td>Wheezing</td>
<td>Rales</td>
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<tr>
<td><strong>Lab data</strong></td>
<td>Non specific</td>
<td>Elevated level of C Reactive Protein</td>
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<tr>
<td></td>
<td></td>
<td>Increased neutrophil</td>
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<tr>
<td><strong>PFT</strong></td>
<td>Obstructive lung disease</td>
<td>Restrictive lung disease</td>
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<td><strong>FEV1/FVC</strong></td>
<td>Decreased</td>
<td>Normal</td>
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<tr>
<td><strong>TLC</strong></td>
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<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 (expiration phase) Mosaic perfusion Bronchiectasis Bronchial wall thickening Centrilobular nodules</td>
<td>Consolidation Ground glass opacity Nodules</td>
</tr>
</tbody>
</table>

## Pulmonary Complications: Typical Onset Timeline

<table>
<thead>
<tr>
<th>Day 0 to day +30</th>
<th>Day +31 to day +100</th>
<th>Greater than +100</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary edema</td>
<td>Pulmonary VOD –</td>
<td>Infection</td>
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<tr>
<td>Pleural effusion</td>
<td>pulmonary arterial</td>
<td>BOS</td>
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<td>Idiopathic</td>
<td>hypertension</td>
<td>Chemotherapy</td>
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<td>pneumonia</td>
<td>Acute Respiratory</td>
<td>induced</td>
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<tr>
<td>Diffuse alveolar</td>
<td>Distress Syndrome</td>
<td>pulmonary</td>
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<tr>
<td>hemorrhage</td>
<td>Early BOOP</td>
<td>toxicity</td>
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<tr>
<td>Acute Respiratory</td>
<td>Infection</td>
<td>Radiation</td>
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<tr>
<td>Distress Syndrome</td>
<td>Chemotherapy</td>
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<tr>
<td>Infection</td>
<td>associated</td>
<td>pulmonary</td>
</tr>
<tr>
<td></td>
<td>pulmonary toxicity</td>
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