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Non-infectious Pulmonary Complications:

Diffuse Alveolar Hemorrhage and Bronchiolitis Obliterans Syndrome

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Objectives

1. Discuss the incidence and risk factors for pulmonary complications following SCT
2. Review the diagnosis and management of diffuse alveolar hemorrhage following SCT
3. Review the diagnosis and management of bronchiolitis obliterans syndrome following SCT

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Overview of all Pulmonary Complications

- Most studies are retrospective
- Incidence
  - Approx 40-60%
  - Associated with significant morbidity and mortality
  - Accounts for 50% of all deaths
- Classified as infectious vs non-infectious
- Compared to infectious pulmonary complications, diagnosis of non-infectious pulmonary complications is more difficult

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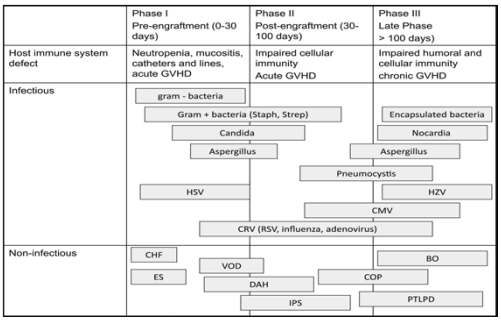
Timeline of Pulmonary Complicatons



From Soubani and Pandya (2010) Hematol Oncol Stem Cell Ther

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4

Pulmonary Complications – Prognostic Factors For Early Severe Pulmonary Complications (< Day +100)

Prognostic

- ** Method of GVHD prophylaxis
  - CYA/MTX increased risk compared to T-cell depletion
- Decreased pre-transplant FEV1 (</80% predicted)
- Auto SCT associated with significantly lower risk

Not Prognostic

- Grades 3-4 GVHD
- Tobacco use
- Age >/50 years
- Sex
- Unrelated donor
- CMV serologic status
- Disease status at transplant
- Pre-transplant DLCO
- TBI

Ho et al (2001) BBMT

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5

Pulmonary Complications – Conventional Allo SCT vs Nonmyeloablative SCT

Is there a difference between nonmyeloablative and conventional allo SCT?

- No difference in overall mortality or pulmonary-related mortality
- In the nonmyeloablative group:
  - trend toward lower incidence of PC in older patients in the early post-SCT period
  - Higher incidence of infectious pneumonias and BOS at later time points

Diab et al. (2012) BBMT

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Pulmonary Complications – Risk Factors – Auto SCT

Independent risk factors associated with pulmonary complications

- Decreased DLCO
- Indication for transplant

Factors associated with mortality

- Sex
- History of pulmonary disease
- Disease status at transplant
- Decreased FVC
- Karnofsky score
- Underlying diagnosis

Afessa et al (2012) Chest

7

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Diffuse Alveolar Hemorrhage (DAH)

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Case Giovanni "Gio"

- 38yo male diagnosed with T-Cell PLL and DLBC NHL in 2/13
- Admitted 3/14 for allo sib SCT with TBI/Cy conditioning
- GVHD prophylaxis with Cya/MTX
- ID prophylaxis starting Day-2 with fluconazole, valacyclovir, and ciprofloxacin
- Post SCT course complicated by febrile neutropenia and mucositis
- On Day +14 reports worsening of his SOB with new 02 requirement. He also reports 2 episodes of bloody sputum with coughing.

9

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DAH

- Syndrome consisting of hypoxia, multilobar infiltrates, and progressively bloody BAL fluid
- Reported incidence has been from 5-12% however recent studies indicate incidence to be 5%
- Despite treatment and supportive care mortality is high at 60-100%
- Patients usually require ICU care and mechanical ventilation
- Death is usually due to multi-organ failure, ARDS, infection or sepsis

10

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DAH – Risk Factors

- No relationship – transplant intensity
- Risk factors
  - Age >40
  - TBI
  - Transplant for solid tumors
  - Presence of:
    - high fevers
    - severe mucositis
    - leukocyte recovery
    - renal insufficiency
    - acute GVHD
    - DMSO
    - Growth factors

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DAH

- Pathogenesis is unclear – possibly damage to alveolar capillary membrane begins during conditioning resulting in release of inflammatory mediators
- Unclear if this is part of a spectrum of conditioning related lung injury or occult infection
- Postmortem exams note the majority of pts have evidence of diffuse alveolar damage
- Incidence often coincides with count recovery – raises the question - does neutrophil influx accentuate injury

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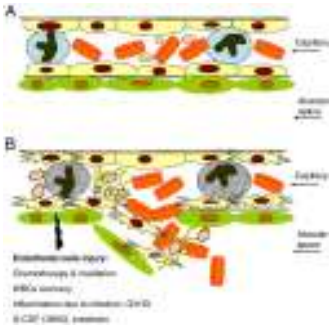
DAH - Pathogenesis



Nadir and Brenner (2012) Blood Reviews

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DAH - Presentation

- Most often occurs within peri-engraftment phase – median of 23 days
- Presentation
  - Dyspnea
  - Nonproductive cough
  - Fever
  - Diffuse pulmonary infiltrates
  - **hemoptysis is rare

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DAH - Diagnosis

- Radiology findings
  - Diffuse interstitial, alveolar or ground glass changes that are more prominent in the perihilar areas and lower lobes
- Radiologic findings appear up to 3 days prior to clinical diagnosis
- Diagnosis by BAL

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DAH – Diagnostic Criteria

1. Evidence of widespread alveolar injury manifested by multilobar pulmonary infiltrates, signs and symptoms of pneumonia, and abnormal physiology with a widened A-a gradient
2. BAL showing progressive bloodier return from 3 separate subsegmental bronchi or more than 20% hemosiderin-laden macrophages on examination of the BAL fluid. If surgical biopsy performed, >30% alveolar surface of examined lung tissue covered by blood
3. Absence of infection compatible with the diagnosis

Afessa et al (2002) Respir Crit Care Med

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Is it DAH or Infection-Associated Hemorrhage (IAH)?

- Similarities exist between DAH and IAH
- Can be difficult to clinically distinguish between the two
- This suggests that these 2 entities may share a similar disease process
- The use of steroids in the setting DAH and IAH has been shown to have a similar 60-day mortality
- There is always the concern that high-dose steroids may increase the risk of infection or worsen IAH
- Most studies on DAH include IAH patients in their samples

17

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Comparing DAH and IAH

- Prospective review of 1919 patients comparing pts with DAH and IAH presenting with similar symptoms
- 45 pts with DAH and 71 with IAH
- methylprednisolone 500mg bid x3 days →250 mg bid x3 days → 125mg bid x3 days → 60mg bid x3 days → 60mg daily until tapered off over 2 month period
- Outcomes:
  - Older age, allo donor source, myeloablative conditioning, severe aGVHD independently predictive of increased risk of AH
  - Probability of 60 days survival16% DAH and 32% IAH
  - All but 20 pts treated with high dose steroids
  - Pts receiving steroids had a 60 day survival of 26% compared to 25% without steroid

Majhail et al (2006) BBMT

18

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DAH - Management

- Most studies have been retrospective
- High-dose steroids have been the primary therapy
- Treatment and dosing strategies can vary widely
- The early addition of an antifibrinolytic agent may be associated with lower mortality
- Most reports include infection-associated hemorrhage in their samples

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DAH Management

Supportive Care

- Oxygen
- Mechanical ventilation
- Blood product administration
  - Blood
  - Platelets
  - FFP

Therapies

- Steroids
- aminocaproic acid – inhibits plasmin impeding fibrinolysis
- rFVIIA – promotes hemostasis via both a tissue factor-dependent pathway at sites of endothelial injury and tissue factor-independent mechanism directly activating factors IX and X on the surface of activated platelets

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DAH Management – Steroid Dosing

- High dose steroids remain first line therapy
- Metcalf et al. Am J Med (1994)
  - 3 treatment groups
    - Supportive care
    - Low dose steroids (<30 mg)
    - High dose steroids (>30 mg)
- Raptis et al. BMT (1999)
  - 74 pts receiving allo SCT for hem malignancies – 4 with DAH
  - Methylprednisolone 250mg-1.5 GM/day x 4 days with slow taper
- Lewis et al. BMT (2000)
  - 23 cases of DAH in pts with heme malignancies receiving allo SCT
  - Methylprednisolone 250 mg- 2GM/day
- Chao et al. An of Int Med (1991)
  - 4 pts receiving auto SCT for lymphoma
  - 1 GM/day x 3 days followed by taper every 3 days

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DAH Management – Aminocaproic Acid

- Wanko et al. BBMT (2006)
  - 14 pts with DAH treated with methylprednisolone (250-1GM/day). Subgroup of 8 treated with aminocaproic acid 1000mg IV q6 hrs.
  - Steroid + aminocaproic acid group
    - 44% 100-day DAH mortality
  - Steroid-only group
    - 83% 100-day mortality

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Low-, Medium-, and high-dose steroids with or without aminocaproic acid in adult hematopoietic SCT patients with diffuse alveolar hemorrhage Rathi et al. (2014) BMT

- Retrospective review 119 adult SCT patients treated for DAH
- Pts subdivided into low(<250mg/day), medium(250-1000mg/day) and high-dose(>/1000mg/day) steroid groups with or without ACA
- Primary objective was 30, 60, and 100 day ICU and hospital mortality
- Overall mortality on day 100 was 85%
- **35% of this population had positive respiratory cultures**
- Outcomes:
  - In the steroid + ACA groups there was not significant differences in 30,60,100 day mortality
  - In the steroid-only group the lower dose steroid had lower ICU and hospital mortality
  - In multivariate analysis – medium and high-dose steroid were associated with higher ICU mortality compared to low-dose group

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DAH– Activated Factor VII

- Retrospective review 22 patients
- 21 pts required ICU care and 17 required intubation
- All pts received 35-120 mcg/kg rFVIIa q2hrs until hemostasis achieved or treatment judged inadequate. Median dose to control bleeding was 5 +/- 3mg
- 8 pts died
- Deaths were due to multi-organ failure, sepsis, and progressive underlying disease
- No adverse thrombotic events were observed
- Conclusion - effective in achieving hemostasis it did not treat the underlying condition

Pathak et al. (2014) Am J Respir Crit Care Med

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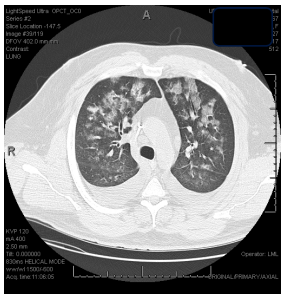
DAH – Back to the Case

- HRCT Scan 4/15/14
- BAL 4/16/14
  - "scattered blood noted throughout the airways, particularly on the right. BAL of RML revealed bloody return"
- Cytology/Cultures 4/16/14
  - "Negative for malignant cells. Alveolar macrophages, bronchial epithelial cells, RBCs and scattered neutrophils present"
  - Negative for pneumocystis and fungal elements
  - Cultures negative



25

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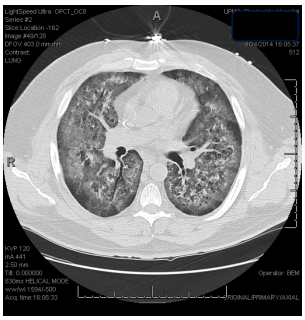
DAH – Back to the Case – second CT 4/24/14



26

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Bronchiolitis Obliterans Syndrome (BOS)

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BOS - Patient Case

- 31yo female diagnosed with AML and s/p MUD SCT in 8/07
- Post SCT course complicated by cGVHD and multiple pulmonary infections
- Presented in 2010 with worsening SOB. PFTs and high resolution CT scan (HRCT) c/w BOS
- Treated with high-dose steroids with improvement in her symptoms

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BOS Definition/Description

- Defined as a serious complication of allo SCT characterized by airflow obstruction and pathologically characterized by progressive fibrosis and obliteration of the bronchioles that develops in the setting of cGVHD
- Most common late non-infectious pulmonary complication following allogeneic SCT
- Incidence varies – 2 to 30 % with a mortality from 27%-90%
- Significant effect on QOL
- Treatment of BOS associated with significant morbidity

29

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BOS – Risk Factors

- Older age of donor or recipient
- Greater degree of HLA mismatch
- TBI
- Presence of GERD
- Decreased gamma globulin levels
- Busulfan-based conditioning regimen
- GVHD prophylaxis
- Underlying hematologic disease
- Tobacco use
- Acute GVHD
- Transplant type
- Increased use of PBSC
- Development of RSV or parainfluenza virus infection within the first 100 days of SCT
- Presence of AFO pre-SCT (FEV1/FVC <0.7)
- ****Association between development of alliterative bronchiolitis and the presence of active cGVHD**
- Risk appears to be highest with progressive cGVHD vs quiescent cGVHD or de novo cGVHD

Barker et al. (2014) NEJM

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BOS - Presentation

- Late complication
- Usually presents after 100 days
- 80% of cases present between 6 and 12 months
- Presentation is usually insidious
- Symptoms
  - Dry cough (60-100%), dyspnea (50-70%)
  - Wheezing
  - Fever rare unless associated with infectious process
  - ~20% are asymptomatic and diagnosis is suspected based on PFTs
- Clinical course
  - Variable
  - Most pts present with slow progressive airflow obstruction (AFO) with episodes of exacerbation of AFO

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BOS - Pathogenesis

- Most important mechanism is probably an alloreactive immune process in which donor T-lymphocytes target epithelial cells of the bronchioles leading to an inflammatory reaction
- Pathogenesis - several other theories exist
  - Result of lung injury precipitated by conditioning regimen
  - Result of infectious etiology
  - Recurrent micro aspirations

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BOS – Pathogenesis - Barker et al. (2014) NEJM

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BOS - Diagnosis

- Clinical Assessment
- Pulmonary function testing (PFT)
- Chest imaging
  - To r/o infectious vs non-infectious etiologies
  - CXR ok as initial assessment, however the major non-infectious syndromes related to transplant require HRCT scan
- Diagnostic procedures
  - Also to r/o infectious vs non-infectious etiologies
  - BAL
  - Lung biopsy

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BOS - PFTs

- PFT measurements fall into 3 categories
  - Spirometry
  - Lung volumes
  - Diffusion capacity
- Spirometry is the main study used to diagnose and follow BOS. The 3 most important measures are:
  - FVC – forced vital capacity
  - FEV1 – forced expiratory volume in 1 second
  - FEV1/FVC ratio – ratio to determine if the pattern is obstructive or restrictive
- Diagnostic criteria for BOS:
  - Evidence of airflow obstruction with FEV1/FVC<0.7 and FEV1 <75% predicted. *Some experts consider a decrease in FEV1 of >/10% from pre-SCT baseline as diagnostic criteria*

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Our Patient's Most Recent PFTs

SPIROMETRY :

		PRE-RX			POST-RX		
Parameter	**Units**	Pred	Best	%Pred	Best	%Pred	%Change
FVC	Liters	3.87	1.93	50	2.17	56	12
FEV1	**Liters**	**3.07**	**1.07**	**35**	**1.17**	**38**	**9**
FEV1/FVC	**%**	**79**	**55**		**54**		**-2**

RESULTS: 10/14/14

- The FVC, FEV1, and FEV1/FVC are reduced. There is no significant response to bronchodilator administration. The diffusing capacity is decreased. The RV is increased.

IMPRESSIONS:

- Severe airway obstruction pattern. No significant bronchodilator response is elicited. The decreased diffusing capacity suggests loss of capillary bed or diffusion block. The elevated RV suggests air trapping. Since the studies of 07/30/2013 the FVC and FEV1 are decreased. The DLCO is unchanged.
- ICD9 DIAGNOSIS:
- 1. Respiratory bronchiolitis interstitial lung disease (516.34)

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BOS - Diagnosis

- Chest xray
  - Early stages – may be normal
  - Later stages – signs of hyperinflation followed by bronchiectasis with dilated and thickened bronchi and areas of scarring
- High resolution CT scan (HRCT) - more sensitive and procedure of choice
  - Findings – air trapping, bronchial wall thickening, bronchiectasis, and bronchial dilations
  - Also can r/o infectious causes
- Bronchoscopy – limited role
- Transbronchial biopsy – not recommended
- Surgical lung biopsy by VATs – if histological confirmation required

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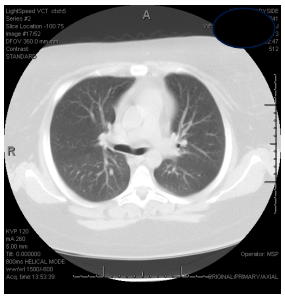
HRCT 4/2008

- HRCT
  - 4/08 - normal



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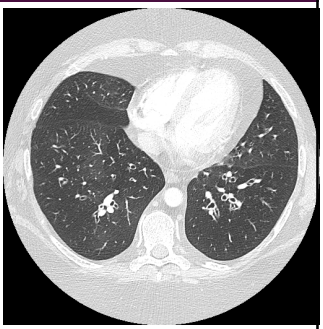
38

HRCT 4/2010

- HRCT 4/10 at diagnosis with BOS
  - IMPRESSION:
    - Findings of obliterative bronchiolitis with bronchiectasis involving all lobes



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39

BOS – Diagnostic Criteria

Suggested Criteria
1. Allogeneic SCT
2. Chronic GVHD
3. Evidence of airflow obstruction with FEV1/FVC<0.7 and FEV1 <75% predicted. *Some experts consider a decrease in FEV1 of >/10% from pre-SCT baseline as diagnostic criteria*
4. Air trapping or small airway thickening or bronchiectasis on HRCT of the chest with inspiratory and expiratory cuts, residual volume of PFT >120% predicted
5. Absence of infection based on clinical symptoms, radiographs, microbiology cultures, sputum cultures or BAL
6. Pathologic confirmation of constrictive bronchiolitis (biopsy not required for clinical diagnosis if all above criteria met)

Chi et al. (2013) Chest
Majhail et al., (2012) BBMT

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BOS - Treatment

- Management is difficult and treatment does not result in complete improvement in lung function
- The goal of therapy is stabilization
- Main Treatment:
  - Systemic corticosteroids
    - Prednisone 1 to 1.5 mg/kg daily for 2-6 weeks. If clinical and physiologic stabilization - taper every 2 weeks over 2 to 3 months
  - Immunosuppressive agents
    - Calcineurin inhibitors
- Treatment recommended for 3-12 months

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BOS – Treatment - FAM

- Treatment
  - **F**luticasone – inhaled bid
  - **A**zithromycin – 250mg po qmon-Wed-Fri
  - **M**ontelukast – 10mg po daily
- Based on reports in SCT and lung transplant literature that suggest FAM may have anti-inflammatory and antifibrotic effects
- Norman et al (2011 BMT):
  - Retrospective review over 6 months
  - 8 pts with BOS compared to 14 matched historical controls
  - 6 month prednisone exposure in FAM-treated pts 1819mg (0-4036mg) compared to 7163mg (6551-7829) control group
  - FEV1 change in FAM group was 2% compared to 1% in the control group
  - Suggests FAM group may be spared to comorbidities associated with steroids

42

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Slide 40

c1 Cheryl, 1/23/2015

BOS – Treatment – Extracorporeal Photophoresis

- Has been reported as an effective treatment for lung transplant complicated by BOS
- Lucid et al. (2011) BMT
  - 9 patients – median follow-up of 23 months
  - Patients treated with 2 pheresis treatments per week for 3-4 weeks and then decreased to and every 2-3-week interval with goal to get to a q 4-week frequency
  - Median number of drugs used was 5 (range 2-7) and included immunosuppressive therapy and FAM
  - 6 of 9 responded to ECP after median of 25 days (range 20-958 days)
  - Response defined as symptomatic improvement, decreased dependency on 02 and improvement in PFTs

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BOS – Other Strategies

- Limited data:
  - Few reports using anti-TNF alpha monoclonal antibodies such as infliximab
  - Imatinib mesylate
  - rituximab
  - Intravenous immunoglobulins

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BOS – Supportive Treatment and Management of Advanced Cases

- Infection prophylaxis
  - Against P jiroveci, fungus, and CMV in high risk patients
  - Appropriate vaccinations against influenza and pneumococcus
  - Prompt treatment of pulmonary infections
- Long-term 02 therapy
- Pulmonary rehab
  - Consists of:
    - Exercise training
    - Nutritional counseling
    - Education on lung disease or condition and how to manage it
    - Energy-conserving techniques
    - Breathing strategies
    - Psychological counseling and/or group support
  - Tran et al. (2012) BBMT – noted significant improvement in physical functioning score, improved 6-minute walk distance, subjective symptoms of dyspnea, and exercise tolerance

45

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BOS – Supportive Treatment and Management of Advanced Cases

- Consider lung transplant
  - Several case reports exist
  - Cheng et al. (2014) BBMT
    - Can prolong survival in pts with end-stage pulmonary complications
    - Patient factors associated with good long-term outcome: young age, at least 2 years post-SCT free of relapse, and lack of end-organ dysfunction or manifestations of cGVHD that require treatment with immunosuppresses

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ASBMT Guidelines - "Recommended Screening and Preventative Practices for Long-Term Survivors after Hematopoietic Cell Transplantation" Majhail et al. (2012) BBMT

1. Routine clinical assessment by H&P exam for pulmonary complications recommended for all patients at 6 months, 1 year, and yearly thereafter
2. Some experts recommend earlier and more frequent clinical assessment including PFTs in pts with cGVHD
3. History of smoking should be assessed and pts who smoke or at risk for passive smoking should be counseled regarding smoking cessation
4. In pts with signs or symptoms of lung compromise, PFTs and focused radiologic assessment should be performed as clinically indicated. F/U evaluations should be guided by clinical circumstances for pts with recognized defects

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BOS - Outcomes

- Progressive disease leading to irreversible AFO
- Decline is usually slow over several months to years. Some patients can have rapidly progressive BO leading to respiratory failure
- Exacerbations can be associated with temporary worsening of lung function
- Aggressive therapy results in improvement in only 8-20% of patients
- Aim to stabilize and prevent further drops in FEV1
- Mortality
  - 9% at 3 years
  - 12% at 5 years
  - 18% at 10yrs

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BOS - Outcomes

- Factors associated with increased mortality:
  - Rapid deterioration of FEV1 – more than 10% annually
  - Age >60
  - Progressive cGVHD
  - Underlying disease relapse
  - History of respiratory viral infection
  - Failure to respond to the primary treatment regimen
- Factors likely NOT associated with prognosis:
  - Presence of AFO prior to SCT
  - Source of stem cells
  - Degree of matching
  - CMV serologic status
  - Type of GVHD prophylaxis

49

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Is it BOS or BOOP (now known as COP)?

- BOOP = Bronchiolitis obliterans organizing pneumonia now known as COP = Cryptogenic-organizing pneumonia
- Distinct entity described following auto and allo SCT
- Develops earlier than BOS
- Clinical presentation of COP can be similar to BOS
- Presentation usually acute with 2 weeks of fever, nonproductive cough, and dyspnea

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Comparison Between BO and BOOP/COP

Features	BO	COP
Incidence	0-48%	<2%
SCT	Allogeneic	Allo and auto
Onset	Late (1yr)	Usually first 100 days
Clinical presentation	Cough, dyspnea, wheeze	Cough, dyspnea, fever
Radiologic Findings	Normal; hyperinflated, air trapping, bronchiectasis	Patchy consolidation, ground glass opacities, nodular opacities
PFT	Obstructive; normal DLCO	Restrictive; decreased DLCO
Diagnosis	Clinical, radiographic, physiologic	Tissue biopsy
Histopathology	Fibrotic plugs obliterating bronchioles with inflammation and scarring; spare alveoli and alveolar ducts	Granular plugs of bronchioles, extending into alveoli; interstitial inflammation and fibrosis
Treatment	Steroids and immunosuppressives	Steroids
Outcome	Poor response to therapy; progressive disease with high mortality	Good response to therapy; potentially reversible

Soubani et al. (2010) Hematol Oncol Stem Cell Ther

51

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Back to the Case…

- She is currently 02 dependent
- Have had a difficult time tapering her steroids lower than 20 mg daily and has required insulin with her steroids
- Have not been successful in attempts to try other therapies due to her social situation
- Lots of adherence issues

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52

Thank You for Your Attention

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53