PULMONARY INFECTIONS IN HEMATOLOGICAL MALIGNANCIES & POST STEM CELL TRANSPLANT SETTING
15-07-2005

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Hemopoietic stem cell transplant

Types:
- Allogenic
- Autologous

Source:
- Bone marrow
- Peripheral blood after priming with G-CSF
- Umbilical cord
Process

- Conditioning of recipient:
  - high dose chemotherapy
  - ± total body irradiation
- Infusion of stem cells
- Engraftment:
  - ANC>500/cc and sustained platelet count >20,000/cc that lasts for 3 consecutive days without transfusions
  - 3 weeks after HSCT
Immunosuppressive therapy

- After allogenic transplantation
- For GVHD prophylaxis
  - Methotrexate
  - Cyclosporin
Division of post-transplant period

- **phase 1** (the first 30 days)
  - Prolonged neutropenia: less severe in autologous SCT
  - Disruption of mucosal barriers following cytoablative therapy

- **phase 2** (Days 31 to 100): depressed cell mediated and humoral immunity

- **phase 3** (more than 100 days): chronic GVHD and GVHD prophylaxis
Phase 1

- Gram-negative bacilli,
- Streptococci
- *Staphylococcus epidermidis*,
- *Aspergillus* spp
- *Candida* spp
- HSV

NON INFECTIOUS
- Pulmonary edema
- DAH
- Drug reactions
Phase 2

- *S. epidermidis*,
- *Aspergillus* spp,
- *Candida* spp
- CMV
- EBV
- *Pneumocystis jirovecii*

NON INFECTIOUS
- Idiopathic pneumonia syndrome
- Drug reactions
Phase 3

- VZV
- Encapsulated bacteria
- Tuberculosis
- NTM
- Nocardia

NON INFECTIOUS
- Bronchiolitis obliterans
- BOOP
- Chronic GVHD
- Secondary malignancies
Bacterial infections

- Neutropenia: bacteremia
- Mucositis and use of opiates predispose to aspiration
- Corticosteroid therapy used to treat Acute GVHD
- Use of various intravascular devices
Bacterial infections

- Increase in gram-positive and polymicrobial (3X) infections
- Decrease in documented gram-negative infections from 60% in 1986 to 21% in 2002
- *Escherichia coli*, *Pseudomonas aeruginosa*, and *Klebsiella* spp.: constant
- Increase in percent of MRSA infection over the time
- Progressive rise in rate of resistance of enterococci to vancomycin

- Gram-positive
- Gram-negative
- Polymicrobial
- Anaerobic

*Approximately 90% of patients studied.
Adapted from Rolston. ECCMID 2003. Glasgow, Scotland. Poster 678.
Aspergillosis

• Bimodal onset: 1\textsuperscript{st} peak median 16 d
  2\textsuperscript{nd} peak median 96 d
• Symptoms triad: dyspnea, pleuritic chest pain, and hemoptysis
• Diagnostic yield of FOB low: <50%
• To distinguish infection from contamination, lavage from affected area may be compared with unaffected area
Invasive Aspergillosis

Underlying Diseases

595 Patients

- Solid Transplant 9%
- AIDS 8%
- Other Immune 6%
- Pulm 9%
- Other 5%
- None 2%
- BMT/Allo 25%
- BMT/Auto 7%
- Hematologic 29%

Invasive Aspergillosis

Site of Infection

595 Patients

- Pulmonary: 56%
- Disseminated: 19%
- Other: 9%
- Sinus: 5%
- Skin: 5%
- CNS: 6%

CNS = central nervous system.
CT scan

- dense, well-circumscribed pulmonary infiltrate
- "halo sign": present in all on day 0
  22% by day 7
- "crescent sign" (an air crescent caused by contracting infarcted tissue): appears day 3
  28% day 7
  63% day 14
Airway-invasive aspergillosis

- Patchy, peribronchial consolidation
- Small ill defined nodules centrilobular nodules or tree-in-bud
- GGO
- Lobar consolidation
- Yield of BAL high
Galactomannan assay

- Early detection: even before clinical features
- Sensitive (80%) and specific (90%)
- Negative test does not rule out and positive test should be judged in clinical setting
- Check same specimen: if first sample + follow with 2nd specimen before therapy
Galactomannan assay

- When to use:
  - pts at increased risk  ?  biweekly monitor
  - assess response to Rx

False +ve

- Children
- Allo SCT (1st 2wks)
- Piperacillin-Tazobactam

Patients on antifungal Rx/Px: false –ve

Urine: lower sensitivity than serum
Treatment of fungal infections

• **Definite**: proven infection
• **Empiric treatment**: fever + neutropenia + no response to proper antibiotics
• **Pre-emptive Rx**: similar to empiric + increased evidence of infection
• **Prophylaxis**
Voriconazole vs AmB

- Randomized, unblinded, multicenter trial
- Definite or probable aspergillosis n=277
- Complete or partial response
  - Voriconazole: 53%
  - Amphotericin B: 32%
- Statistically significant difference 21%
- Significant difference in survival
- Fewer adverse effects in Voriconazole group

Herbrect et al. *NEJM 2002*
Voriconazole group

Amphotericin B group

P = 0.02

Patients Surviving (%)

Weeks

NO. AT RISK

Voriconazole 144 131 125 117 111 107 102

Amphotericin B 133 117 99 87 84 80 77
Empiric antifungal therapy: is Amphotericin the only answer?

- open, randomized, controlled, multicenter trial
  - 384 neutropenic patients with cancer and persistent fever unresponsive to antibiotics
  - Itraconazole safe and effective as empirical therapy for suspected invasive fungal infection in febrile neutropenic patients


- Voriconazole, Lipid AmB, Capsofungins: have not demonstrated complete success as empiric Rx
Candida

- 50% of disseminated disease have pulmonary involvement
- Symptoms of pulmonary involvement are cough, purulent expectoration, hemoptysis
- Most important clue is the presence of disseminated disease
Radiology

- U/L or B/L segmental or non-segmental consolidation
- Diffuse nodules, rarely miliary
- Pleural effusion 20%
- Screening scan for hepatosplenic candidiasis
Treatment

- Amphotericin B (AmB) (0.5-0.6 mg/kg/day)
- Fluconazole (400 mg/day)
- *Candida glabrata*: resistant; HIGH DOSE AmB (0.7 mg/kg/day)
- *C krusei* > 1 mg/kg/d AmB
- Caspofungin
- Voriconazole
- Itraconazole?
Fluconazole prophylaxis

- 356 autologous and allogeneic HSCT
- Fluconazole (400 mg/day) vs placebo
- From the start of the conditioning period for a maximum of 10 weeks
- Systemic fungal infections: 3% vs 16%
- Fewer infection related deaths
- No effect on overall mortality

Goodman et al. *NEJM* 1992

- Fluconazole (400 mg/day for 75 days) does improve overall survival

Slavin et al. *J Infect Ds* 1995
Long-Term Fluconazole Prophylaxis

Fluconazole administration

- BSI and tissue infection
- Candidiasis-related death

Probability

Years After Transplant

Fluconazole
Placebo

0.00 0.10 0.20 0.30 0.40 0.50
Zygomycosis

- Much less common than aspergillosis
- Occur in allograft patients during pre-engraftment or with corticosteroid therapy used to treat GVHD.
- Treatment is highest tolerable dose of AmB
- Voriconazole is not effective
Known gaps in antifungal coverage

- Fluconazole: *C. glabrata* dose dependent
  - *C. krusei*
- AmB: *Aspergillus terreus*
  - *Fusarium, Scedoporiunm*
- Capsofungin: *Cryptococcus*
- Voriconazole: *Zygomycetes*
**Pneumocystis jirovecii**

- Median time of onset: 60 d from Tx
- HRCT findings:
  - Patchy or diffuse B/L GGO
  - Central, perihilar or upper lobe prominence
  - Thick walled, irregular septated cavities; thin walled cysts
  - Pneumothorax related to cysts
  - Bronchiectasis or bronchiolectasis
Pneumocystis jirovecii

- Diagnosis by BAL in 90%; obviating need of biopsy
- Role of adding steroids is not as clear as in patients with AIDS
- Rx: TMP 5 mg/kg-SMX 25 mg/kg tds
  or Clinda 300mg qid + Primaquin 15mg OD
Herpes simplex pneumonitis

- Most common early infection
- Pulmonary involvement: 5-7%
- Herpes tracheitis or esophagitis commonly associated
- Unexplained pulmonary infiltrates along with mucocutaneous lesions: Tzanck smear
- BAL specimen alone may not be diagnostic: generous tissue biopsy is required
HSV Rx

- Aciclovir: 5-10 mg/kg TDS
- Resistant to Aciclovir: Foscarnet 60 mg/kg TDS
- Duration: 14-21 d

Prophylaxis (until engraftment):
  Aciclovir 200-400 mg QID po
  250 mg/m² TDS iv (severe mucositis)
  500 mg/m² TDS for CMV+HSV
CMV Pneumonitis

- 6-12 wks post SCT; 90% within 100 d; later if Ganciclovir prophylaxis is used
- More common after allogenic transplants
- Fever, dry cough, dyspnea, and hypoxemia with diffuse interstitial infiltrates on CXR
- Other clues: vasculitis, esophagitis, retinitis, atypical lymphocytosis, leukopenia, thrombocytopenia
HRCT in CMV

- Patchy B/L foci of GGO
- Scattered poorly defined nodules
- Reticulation and septal thickening (resolving disease)
- Predilectation to lower lobes
CMV Diagnostic tests

- Serology: to evaluate the patient prior to transplantation
- Conventional cell culture: result by day 11
- Shell vial culture: rapid results on day 2
- Antigenemia (pp65): Direct fluorescent Ag detection. Requires enough no. of cells
- CMV DNA PCR

BMT recipient CMV DNA, PCR is very useful for monitoring patients and the full risk stratification. Positive results in quantitative CMV should lead to antiviral therapy.
Rx of CMV Pneumonitis

- Ganciclovir: 5 mg/kg BD +
  CMV hyperimmunoglobulin for 6 wks
- Maintainence therapy:
  Ganciclovir 6 mg/kg 5 times/wk
  Foscarnet 90 mg/kg 5 times/wk
- Prophylaxis: Started after engraftment
  Ganciclovir 5 mg/kg BD for 7 d
  6 mg/kg 5 times/wk until day 100
Community respiratory viruses

- Increased morbidity and mortality in HSCT/hematological malignancies during community outbreaks
  - RSV 35%
  - Influenza 11%
  - Parainfluenza 30%
  - Rhinovirus 25%
RSV

- High proportion of LRTI
- Typically occurs in winters
- Mortality up to 100%
- Rx: Aerosolized ribavirin with IVIG
- Role of pre-emptive therapy with aerosolized ribavirin in patients with RSV +ve culture
Post Transplant Lymphoproliferative Syndrome

- Incidence: 1.5%
- Occur almost exclusively after allogenic SCT
- T cell depletion: ex-vivo of allograft and in-vivo following anti T-cell therapy for GVHD polyclonal expansion of B cells infected with EBV
- HRCT: multiple nodules peribronchial, subpleural + lymphadenopathy
- Rx: Humanized anti-CD$_{20}$ monoclonal antibody (Rituximab)
Tuberculosis post SCT

- Incidence from India?
- Risk factors
  - Allogenic HSCT
  - Total Body Irradiation
  - Chronic GVHD
- Median time to onset: 150d & 324d in 2 series
- 20 cases of post SCT TB out of total 8013

de la Camara et al. BMT 2000
# Vaccination Strategy for HSCT Recipients

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<th>14</th>
<th>24</th>
<th>Other</th>
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<tbody>
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<td><strong>Haemophilus influenza type b conjugate</strong></td>
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<td>X</td>
<td>X</td>
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<td>Hepatitis B</td>
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<td>X</td>
<td>X</td>
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<td>23-valent pneumococcal polysaccharide</td>
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<tr>
<td>Influenza</td>
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<td></td>
<td>Lifelong seasonal administration, beginning before HSCT and resuming at ≥6 months after HSCT</td>
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<tr>
<td>Meningococcal</td>
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<td>Evaluate for HSCT recipients who live in endemic areas or areas experiencing outbreaks</td>
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<tr>
<td>Inactivated polio</td>
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<tr>
<td>Measles, mumps, rubella</td>
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<td>X</td>
<td>Contraindicated for HSCT recipients</td>
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<tr>
<td>Varicella</td>
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Important Non-infectious D/Ds
Pulmonary edema

- Onset rapid: 2\textsuperscript{nd} / 3\textsuperscript{rd} week post Tx
- Clinical features: orthopnea, wt gain, crackles
- Accompanying hepatic and renal dysfunction
- Radiological: enlarged pulm vs, smooth interlobular septal thickening, smooth peribronchovascular interstitial thickening, smooth subpleural or fissure thickening, patchy GGO
- Response to diuretics
Septic pulmonary emboli

- Setting: intra-vascular catheters

HRCT:
- B/L peripheral nodules in varying stages of cavitation
- Peripheral wedge shaped triangular opacities abutting pleural surfaces with/without cavitation
- Associated pleural and/or pericardial effusion
Diffuse Alveolar Hemorrhage

- More common after autologous SCT
- Onset: 12 d (7-40 d)
- B/L GGO patchy or confluent air space consolidation involving perihilar or lower lung zones
- Successive aliquots of BAL fluid become increasingly hemorrhagic
- Drop in Hb
Engraftment syndrome

- Autologous BMT and peripheral stem cell transplantation
- Symptoms within 5 days after attaining an absolute neutrophil count that is greater than 500
- The median time of onset was 7 days after BMT, with a median duration of 11 days.
- Fever, pulmonary infiltrates, skin rash, and hypoxia
Idiopathic pneumonia syndrome

- Incidence: 10%
- Median time: 2-7 wks
- B/L interstitial thickening associated with GGO and poorly defined small nodular opacities
- KL-6 mucinous HMW glycoprotein is elevated in BAL and serum
TBI and Drug Reactions

- Usually present within 90 d
- Fever, cough, dyspnea, hypoxemia
- Diffuse interstitial infiltrates
- Methotrexate: intestinal pneumonitis
eosinophilic pneumonia
FOB

- Evaluation of pulmonary infiltrates which cannot be identified by imaging, microbiology
- Non responsive to antimicrobial therapy
- Findings at FOB provide specific diagnosis in appx 50% of allogenic HSCT
- TBLB adds to specific diagnosis in <10%
- Bronchoscopy led to change in treatment in 50%
- Establishing a specific diagnosis by FOB does not improve survival

Naimish et al. Chest April 2005
Preparation from BAL samples

- Gram stain
- Giemsa (assessment of macrophages, ciliated epithelium, leucocytes)
- Calcofluor white (fungus & Pneumocystis)
- DIFT for Pneumocystis
- Stain for AFB
- Cytospin: for underlying malignancy
Transthoracic needle aspiration

- W/U of peripheral radiological abnormalities
- Positive diagnosis: 70%
- Correct diagnosis of fungal ds: 65%
- But there is possibility of missing fungal disease: 35%
- Most common complication: Pneumothorax (13-25%)
OLB

- In pts with diffuse infiltrates: OLB required when BAL is non diagnostic or technically impossible
- Suspected invasive aspergillosis: however false negative in 20%
- Non infectious lung infiltrates
- Severe thrombocytopenia:
  - Platelet count <50,000

Complications: 10-15%

2 scenarios where OLB is beneficial
- BOOP
- Discrete solitary pulmonary nodule
D/D of consolidation

- *Pseudomonas* and *E. coli*: airspace consolidation with a patchy bronchopneumonic pattern
- *Klebsiella* and *Enterobacter*: confluent consolidation occupying a segment or lobe; bulging of the interlobar fissure
- *Staph aureus*: patchy consolidation in a bronchopneumonic pattern, bilateral; lung abscesses may develop in areas of consolidation where necrosis has occurred. Pneumatoceles
Consolidation

- *Legionella pneumophila*: multilobar consolidation, nodules
- **Malignancies**: segmental or lobar consolidation, often with prominent air bronchograms. Focal infiltrates may also arise from leukemic deposits
- **Haemorrhage**: widespread consolidation
- **ARDS** (sepsis, cytotoxic drug rxn): widespread consolidation
- Peripheral, subpleural: Plum infarction, Drug rxn
GGO

- HSV
- CMV
- Pneumocystis
- BOOP
- Pulmonary edema
- DAH
- Idiopathic Pneumonia Syndrome
- Lymphoproliferative disorder
Nodules

- Aspergillosis: centrilobular with tree in bud
- Mucormycosis
- Tuberculosis; NTM
- Pulmonary edema: centrilobular without tree-in-bud
- Lymphoproliferative disorder: perilymphathic
- Septic emboli
- Disseminated viral infection
Interlobular septal thickening

- Pulmonary edema: smooth
- Lymphoproliferative disorder: smooth/nodular
- Pneumocystis jirovecii
Infections in CLL

- Multifactorial pathogenesis
  - Hypogammaglobulinemia
  - Decreased CMI
  - Granulocytopenia
    - leukemic marrow
    - drug induced
- Increased incidence with
  - disease progression
  - repeated therapy
Conventional therapies

Chlorambucil, COP, CHOP

- Myelosuppression
  - Pneumonia most common and most severe
  - Bacteremia occurs with neutropenia
  - *S. pneumoniae* > *S. aureus* > *H. influenzae* > *Legionella* > *Salmonella*
  - Localized Herpes common
  - Rare: Mycobacteria, fungi
Nucleoside analogs: Fludarabine

Major infections 50%

- FUO 25%
- Pneumonia 24%
- Atypical: PCJ, TB, Listeria 5%
- Sepsis 11%
  - Gm+ 5%
  - Gm- 6%
- Others: Viral CMV, Herpes
Rituximab

- Profound B cell depletion
- Little effect on Ig or complement
- Occasional, mild neutropenia
- Infections mild responsive to Rx
- Combination with Fludarabine
  - Increase in neutropenia
  - No increased risk of infection
Alemtuzumab

Monoclonal antibody specifically directed against CD52

- This Ag is present on lymphocytes T and B and/or monocytes
- Results in profound prolonged lymphopenia
- CD4 comes back to normal in 2 years
- Decrease in NK-cell cytotoxicity
Infections in CLL treated with Alemtuzumab

- Untreated: Alemtuzumab well tolerated
- Previously treated: increased risk of infection
  - Bacterial pneumonia, bacteremia
  - Viral: HSV, VZV, CMV (20%)
  - Pneumocystosis, fungal & mycobacterial
Infections in Multiple Myeloma

- Defects in humoral immunity
- Infection is the most common cause of death
  - Early: *S. pneumoniae* and other encapsulated bacteria
  - Later: GNB and *S. aureus*
Lymphoma

- Defect in T cell function
- Chemotherapy
- Steroids

Intracellular pathogens:
- *Mycobacterium tuberculosis, M avium*
- Cryptococcosis
- Listeria
- Salmonella
Thank you！