PULMONARY INFECTIONS IN HEMATOLOGICAL MALIGNANCIES & POST STEM CELL TRANSPLANT SETTING

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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 than100 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

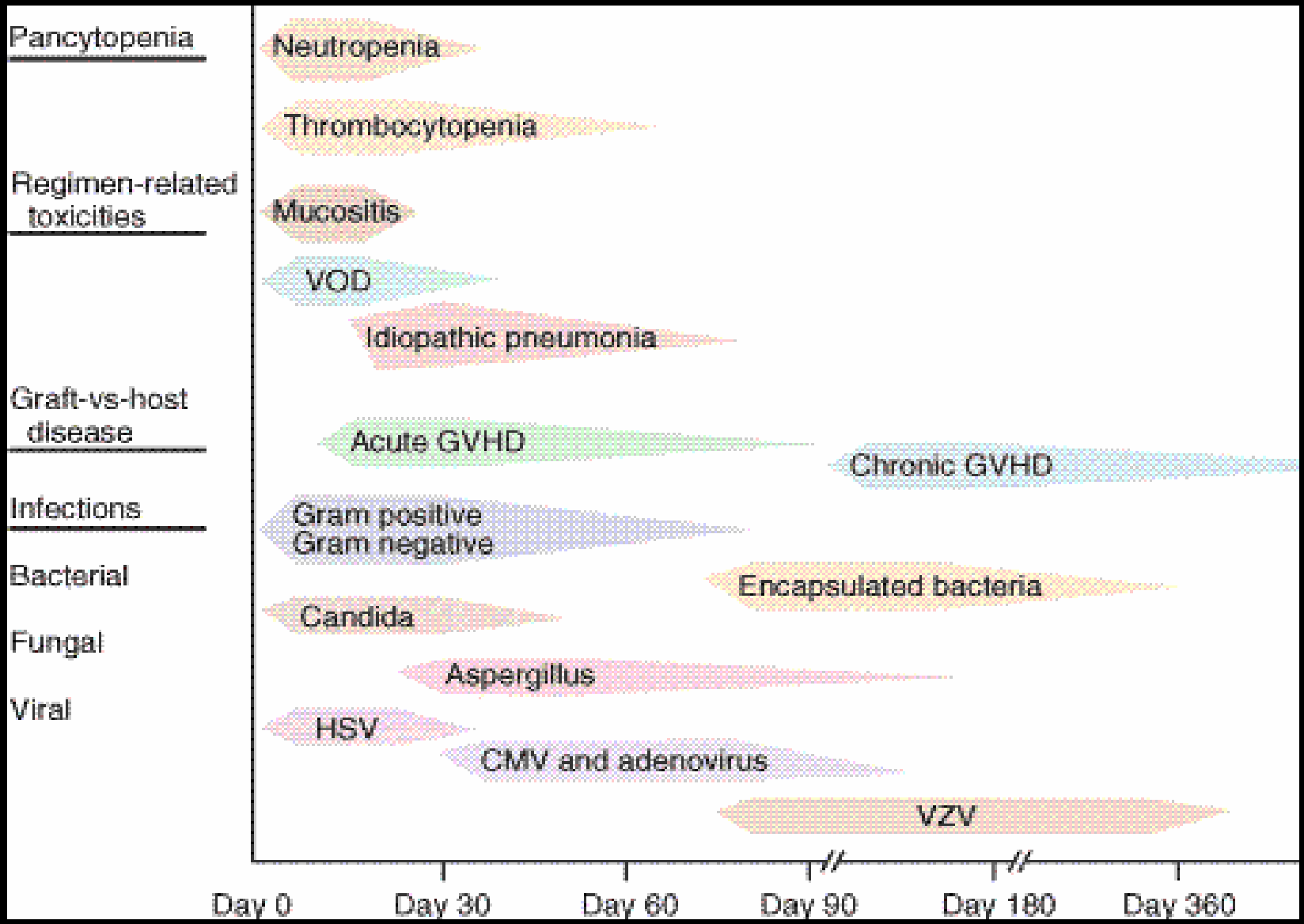
- Idiopathic pneumonia syndrome
- Drug reactions

Phase 3

- VZV
- Encapsulated bacteria
- Tuberculosis
- NTM
- Nocardia

NON INFECTIOUS

- Bronchiolitis obliterans
- BOOP
- Chronic GVHD
- Secondary malignancies


Pancytopenia
Neutropenia
Thrombocytopenia
Regimen-related toxicities
Mucositis
VOD
Idiopathic pneumonia
Graft-vs-host disease
Acute GVHD
Chronic GVHD
Infections
Gram positive
Gram negative
Bacterial
Encapsulated bacteria
Candida
Fungal
Aspergillus
Viral
HSV
CMV and adenovirus
VZV
Day 0
Day 30
Day 60
Day 90
Day 180
Day 360

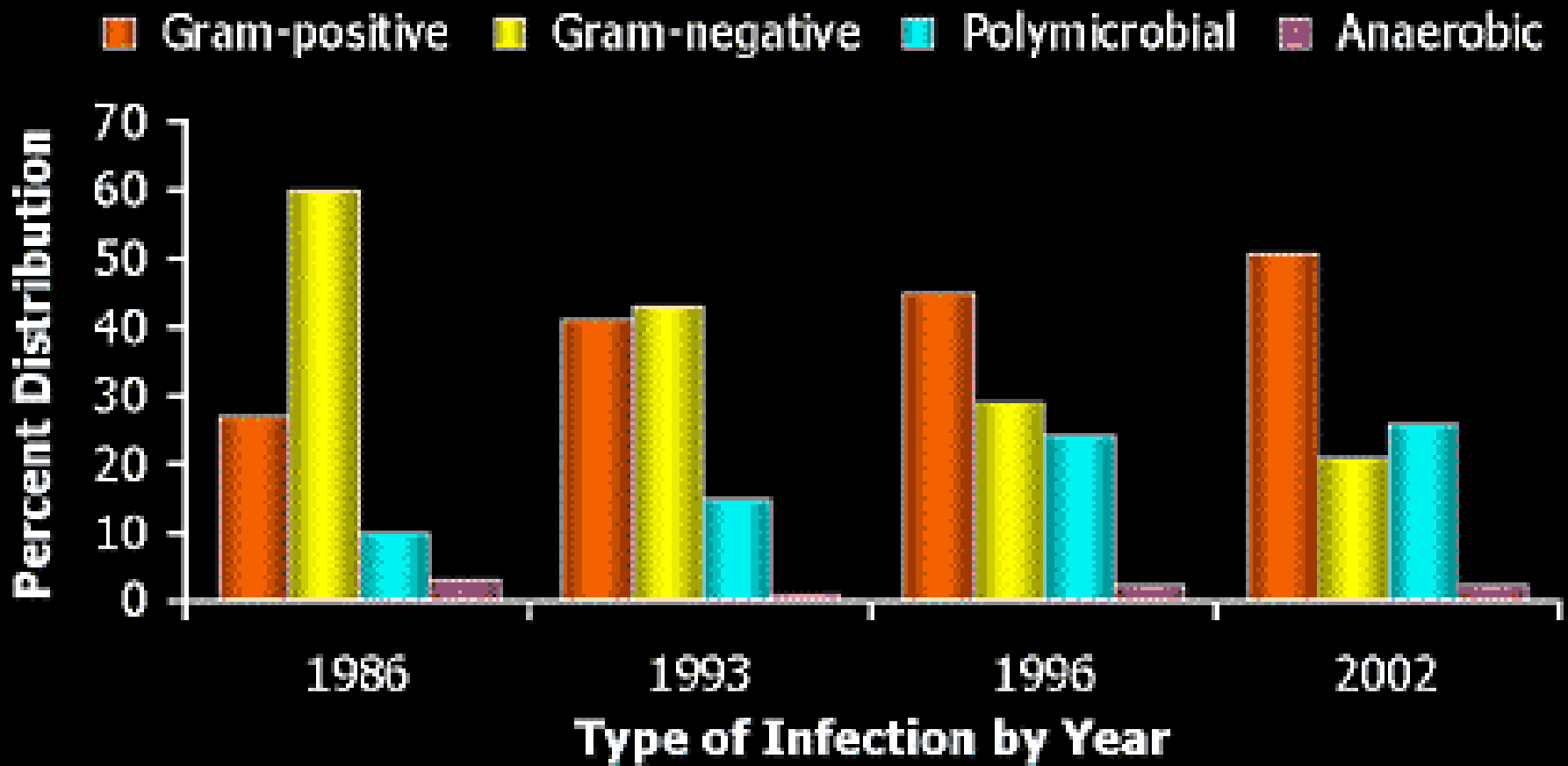
Bacterial infections

- 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

Changing Epidemiology of Bacterial Infections in Patients With Hematologic Malignancies* (1986-2002)



*Approximately 90% of patients studied.

Adapted from Rolston. ECCMID 2003. Glasgow, Scotland. Poster 678.

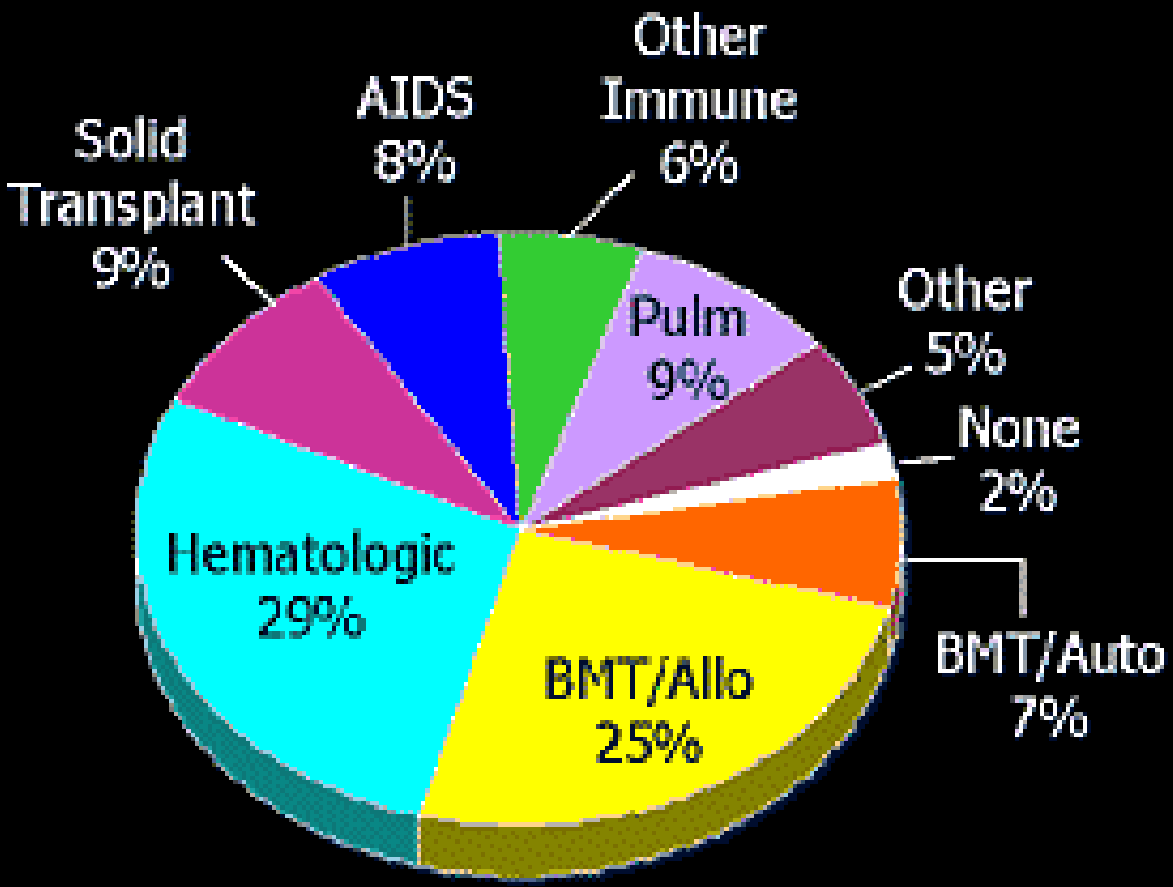
Aspergillosis

- Bimodal onset: 1st peak median 16 d
  2nd 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

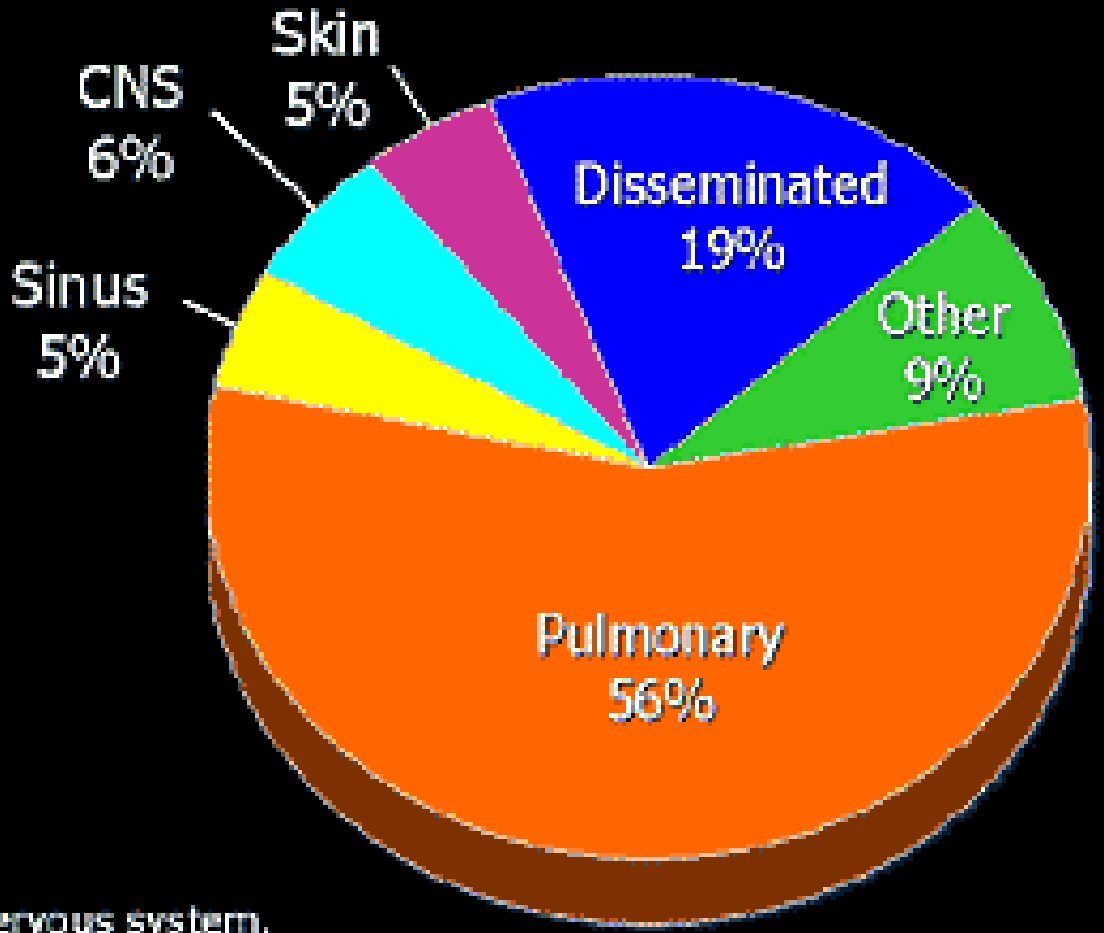


Patterson et al. *Medicine*. 2000;79:250-260.

Invasive Aspergillosis

Site of Infection

595 Patients



CNS=central nervous system.

Patterson et al. *Medicine*. 2000;79:250-260.

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**

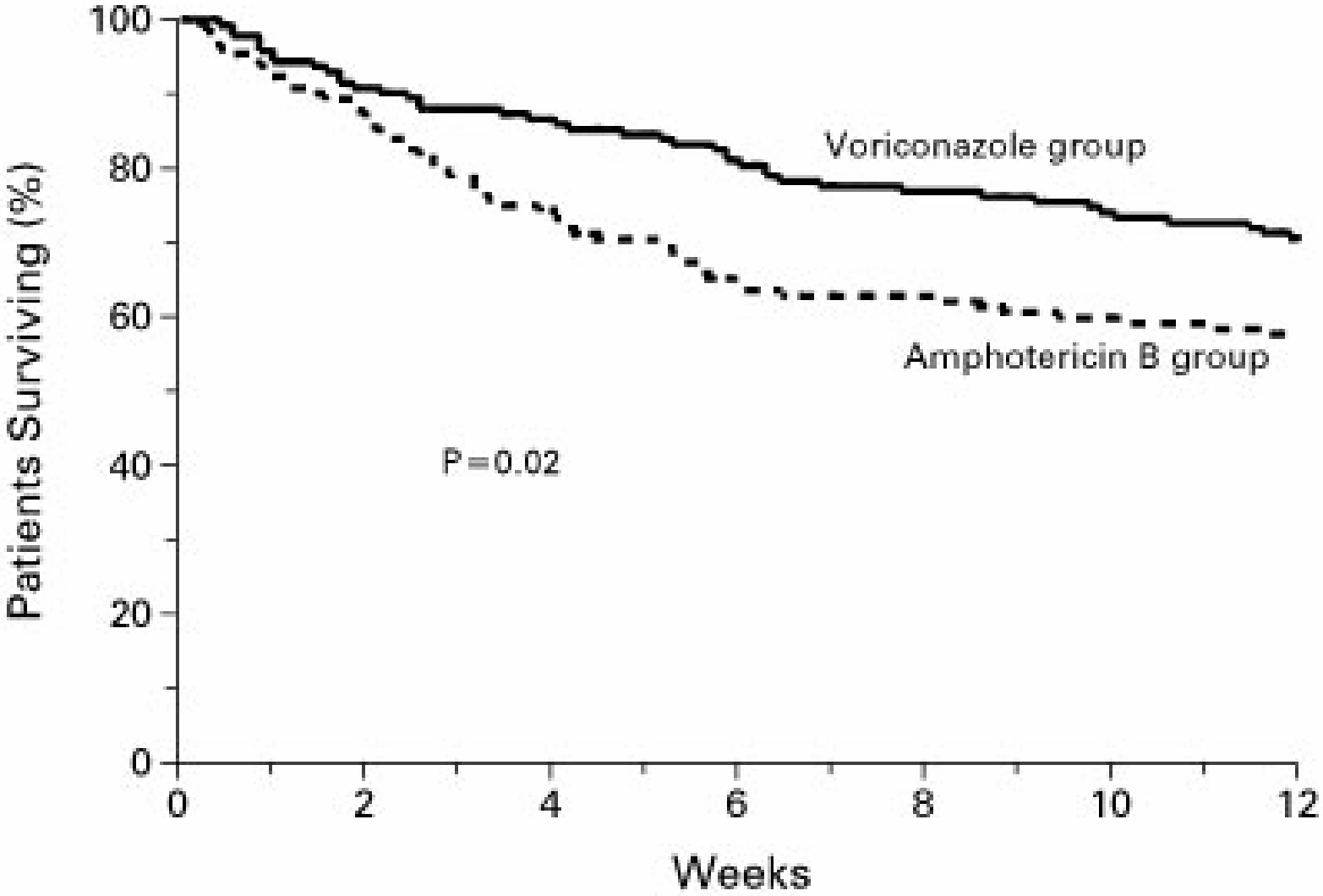
Voriconazole vs AmB

- 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*



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

Boogerts et al. *Ann Int Med* 2001

- ❖ 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

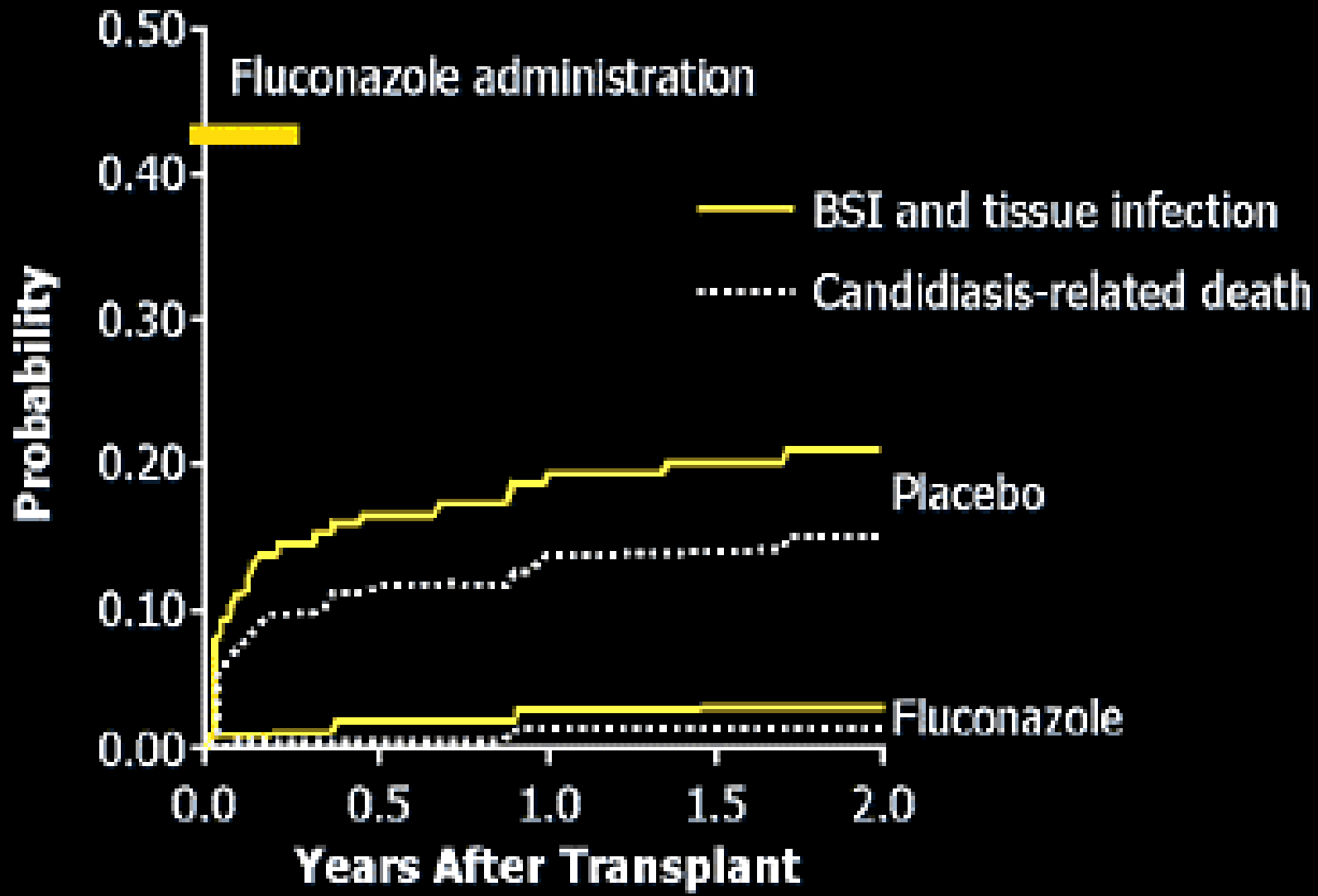
- 356 autologous and allogeneic HSCT
- Fluconazole (400 mg/day) vs placebo
- From the start of the conditioning period for a maximum of 10 weeks
- Systemic fungal infections: 3% vs 16%
- Fewer infection related deaths
- No effect on overall mortality

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



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 depedent, *C krusei*
- AmB — *Aspergillus terreus*, *Fusarium, Scedoporium*
- 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/m^2 TDS iv (severe mucositis)

500 mg/m^2 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

Rx of CMV Pneumonitis

- Ganciclovir: 5 mg/kg BD +

CMV hyperimmuneglobulin 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

Vaccine or Toxoid	Time After HSCT (months) 12	14	24	Other
Tetanus-diphtheria				Should be administered every 10 years
Haemophilus influenzae type b conjugate	X	X	X	
Hepatitis B	X	X	X	
23-valent pneumococcal polysaccharide	X		X	
Influenza				Lifelong seasonal administration, beginning before HSCT and resuming at ≥6 months after HSCT
Meningococcal				Evaluate for HSCT recipients who live in endemic areas or areas experiencing outbreaks
Inactivated polio	X	X	X	
Measles, mumps, rubella			X	
Varicella				Contraindicated for HSCT recipients

Sullivan et al. *Hematology*. 2001;392-421; Centers for Disease Control and Prevention. *MMWR Morb Mortal Wkly Rep*. 2000;49(RR-10):1-125.

Important Non-infectious D/Ds

Pulmonary edema

- Onset rapid: 2nd / 3rd 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 subpleral 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: intestitial 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 pneumophilia*: 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: perilymphatic
- Septic emboli
- Disseminated viral infection

Interlobular septal thickening

- Pulmonary edema: smooth
- Lymphoproliferative disorder: smooth/nodular
- Pneumocystis jirovecii

Infections in CLL

- Multifactorial pathogenesis
  - Hypogammaglobinemia
  - Decreased CMI
  - Granulocytopenia
    - -leukemic marrow
    - -drug induced
- Increased incidence with
  - -disease progression
  - -repeated thearapy

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 !