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BEST HOSPITALS U.S.News & WORLD REPORT NATIONAL CANCER 2014-15

Managing Complications After Hematopoietic Stem Cell Transplantation (HSCT)

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Stem Cell Transplantation

- Objective is to gain an understanding of the general principles behind stem cell transplantation:
  - the different types of transplants
  - how we decide who to offer this treatment to
  - the risks and benefits associated with the procedure

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Stem Cell Transplantation

- Terminology: Hematopoietic stem cells are bone marrow cells that can form all the normal elements seen in blood:
  - white cells, red cells, platelets
  - Characterized by surface markers that allow for purification if desired (CD34)

Stem Cell Transplantation

- Although they are not embryonic stem cells, hematopoietic stem cells can also form other tissue types:
  - Myocardium (help repair heart damage after infarction)
  - Neural tissue (potential treatment of Alzheimer's disease)

Stem Cell Transplantation

- Old- “Bone Marrow Transplant”
  - uses stem cells collected directly from the bone marrow space (pelvis, sternum, ribs)
- New- “Stem Cell Transplant”
  - most transplants now use cells collected from the blood stream after mobilization
- Either type is administered like a blood transfusion to the patient

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Stem Cell Transplantation

- Most transplants are 2 step procedures:
  - patients receive a large dose of therapy that would otherwise destroy both normal bone marrow and immune function
  - After the drugs are cleared from the body, patients receive a stem cell infusion to restore bone marrow and immune function

Autologous Stem Cell Transplantation

- **Definition:** uses stem cells collected from the patient and frozen before the transplant
- **General requirements:**
  - Stem cells can be collected with minimal contamination by cancer cells
  - Evidence shows that patient outcomes can be improved with high dose chemotherapy (best if tumor has shown chemosensitivity

Autologous Stem Cell Transplantation

- Indications
  - Curative: AML, Lymphoma, Hodgkin's Disease, ?ALL
  - Improved survival: Multiple Myeloma, Lymphoma

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Allogeneic Stem Cell Transplantation

- **Definition: uses stem cells collected from a donor**
- **From family (up to 90% of pts)**
  - Identical twin-syngeneic transplant
  - HLA identical or haplo-identical family mem**ber**
- **Alternative donor source (depends on ethnicity)**
  - Registry
  - Umbilical cord blood
- **Chemosensitive disease in most cases**
  - Disease controlled enough to allow development of anti-tumor effect

Allogeneic Stem Cell Transplantation

- What defines a suitable donor:
  - HLA (MLC) compatible (serology or molecular typing)
    - Level of matching depends on clinical scenario and source
    - HLA mis-matches can trigger immune reactions (rejection, graft-vs-host disease)
  - Acceptable health
  - Willingness to donate

Allogeneic Stem Cell Transplantation

- Indications (malignant diseases)
  - CML (now rare due to TKI's)
  - ALL, CLL
  - AML, MDS
  - Lymphoma
  - Multiple myeloma
  - Metastatic Renal Cell Carcinoma

Allogeneic Stem Cell Transplantation

- Indications (non-malignant diseases)
  - Inherited disorders
    - Severe combined immune deficiency
    - Other metabolic disorders
    - Thalassemia (sickle disease)
  - Acquired disorders
    - Aplastic anemia patients who have failed non-transplant therapy (most adults)

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Concepts Of Curative Therapy With Stem Cell Transplantation

- Having a stem cell product available allows doctors to deliver higher doses of treatment (dose-response curve)
- Recipients of Allogeneic transplants sometimes develop immune-mediated ability to kill tumor cells (graft-versus-cancer effect)

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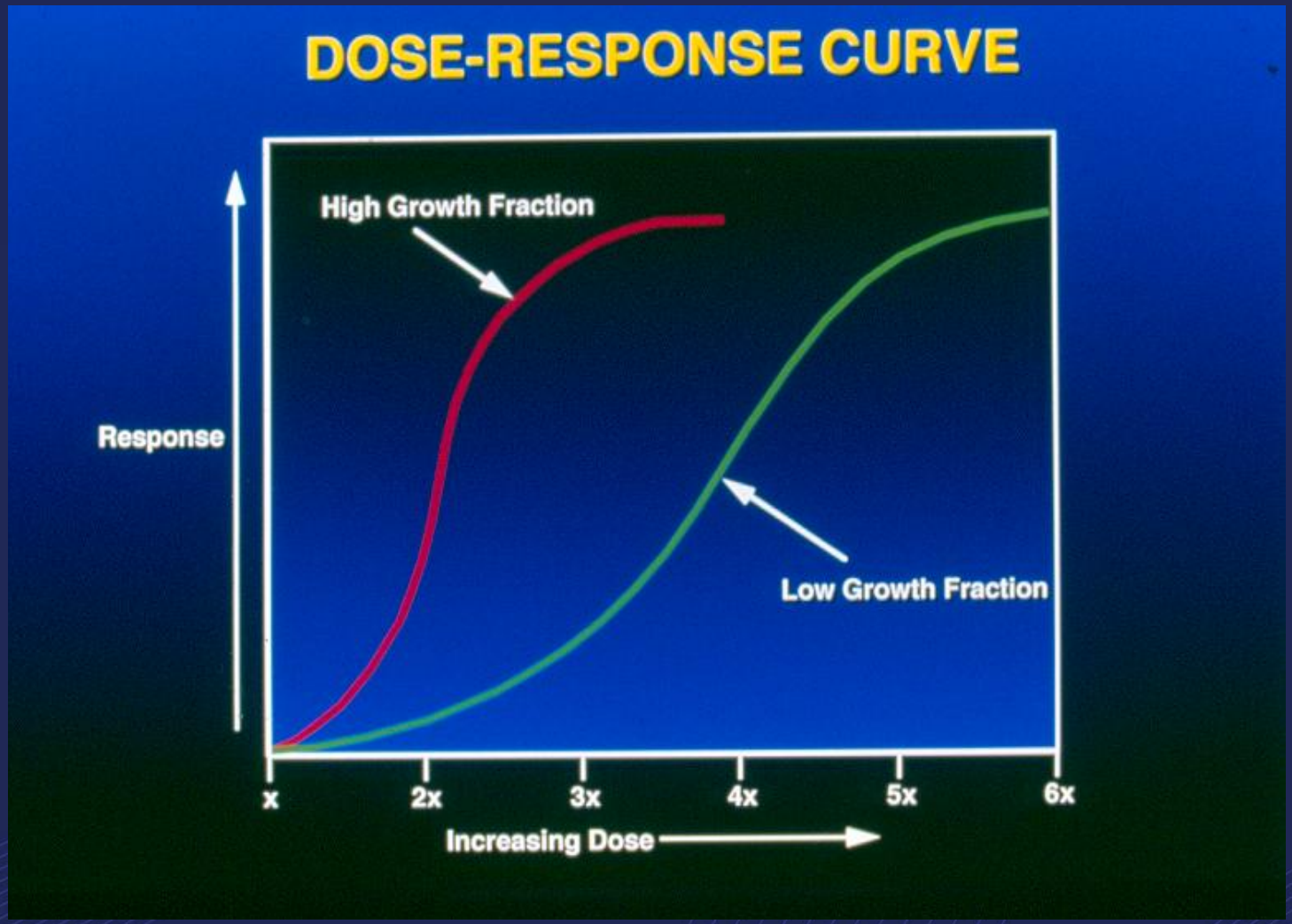
Stem Cell Transplantation



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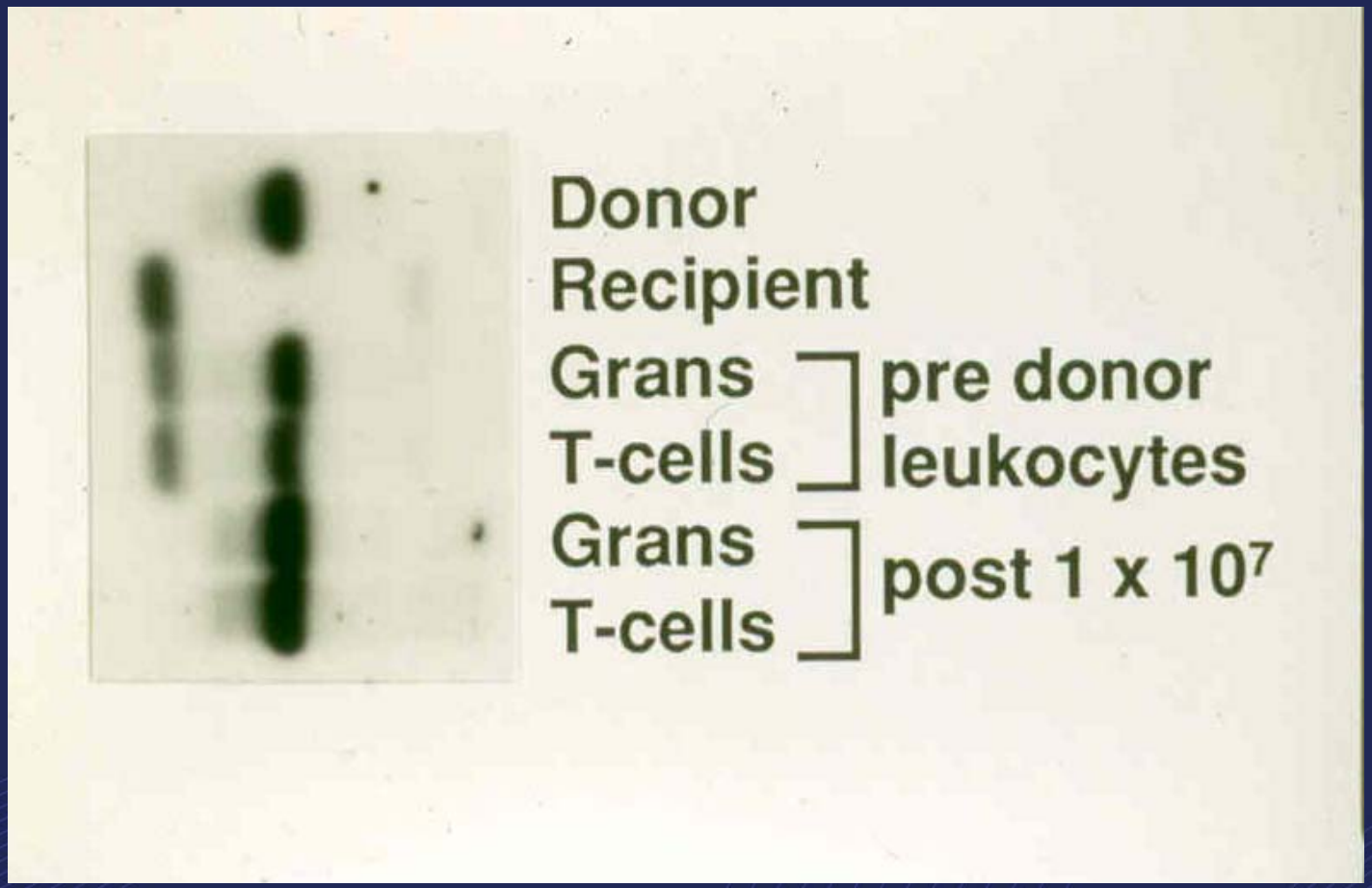
Allogeneic Stem Cell Transplantation
Graft versus Host Reactions



Stem Cell Transplantation

- What drugs do we use?
  - We use agents that have bone marrow suppression as their major side effect (dose-limiting toxicity)
  - These drugs (or radiation) have other side effects that must be considered when choosing patients
  - Allogeneic transplants are now being done with lower doses (Reduced Intensity) to allow immune effect to do work

Stem Cell Transplantation

- Target for treatment: the potential benefit associated with the transplant should at least equal that associated with other treatment options
  - CML: 80% short term survival with or without transplant
  - Aplastic anemia: transplant is riskier, but no long-term survival without it in appropriately selected patients

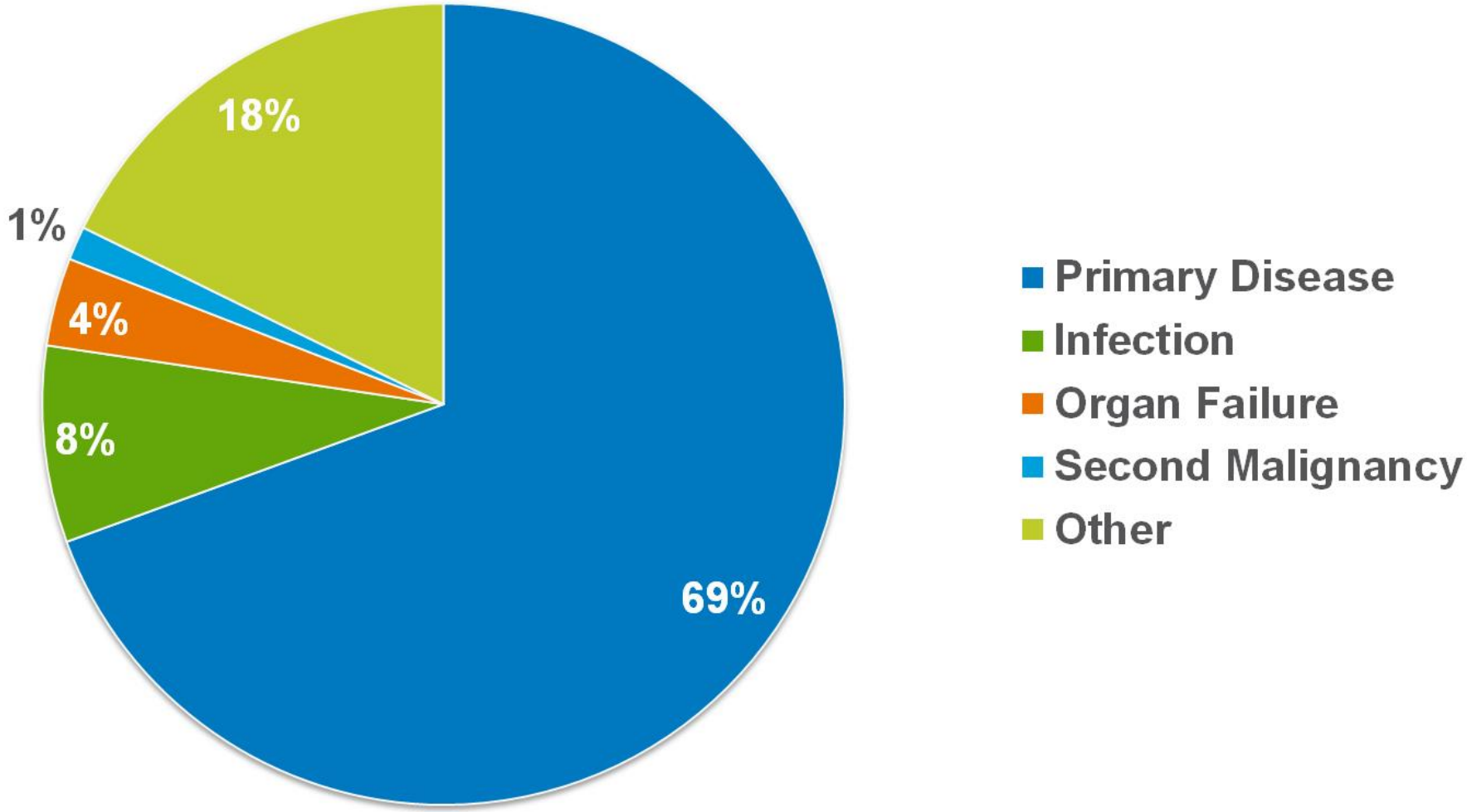
Stem Cell Transplantation

- Patients should be screened for health problems that increase the risk associated with transplantation. The drugs/radiation used can affect other organ systems, including:
  - lungs
  - heart
  - liver

Stem Cell Transplantation

- Social history is important to screen for:
  - smoking- increased risk of heart or lung disease
  - drinking- increased risk of liver disease
  - high-risk behavior- increased risk of HIV, hepatitis, herpes viruses
  - occupational exposure- lung disease

Causes of Death after Autologous Transplants done in 2010-2011



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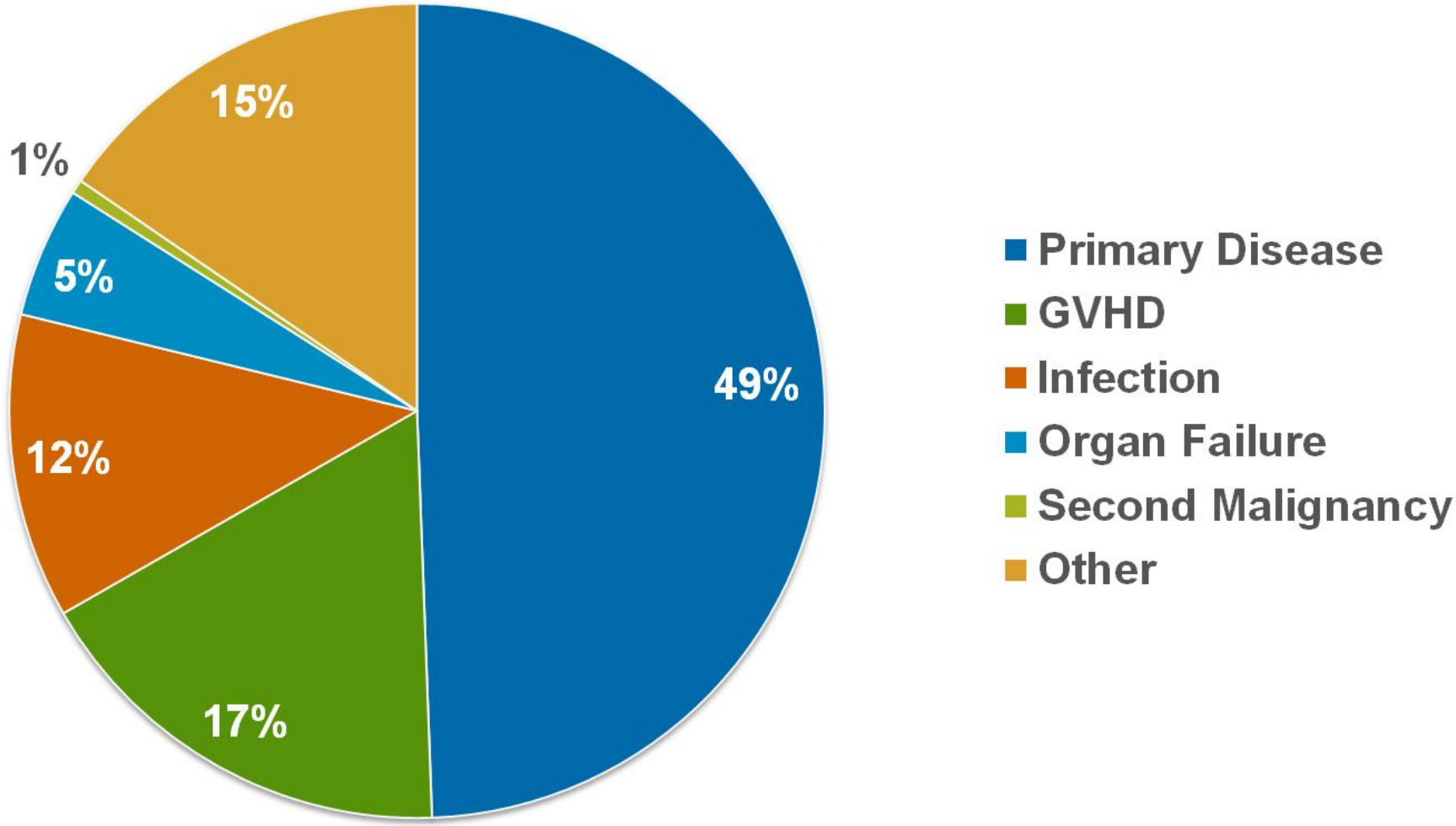
Causes of Death after HLA-identical Sibling Transplants done in 2010-2011



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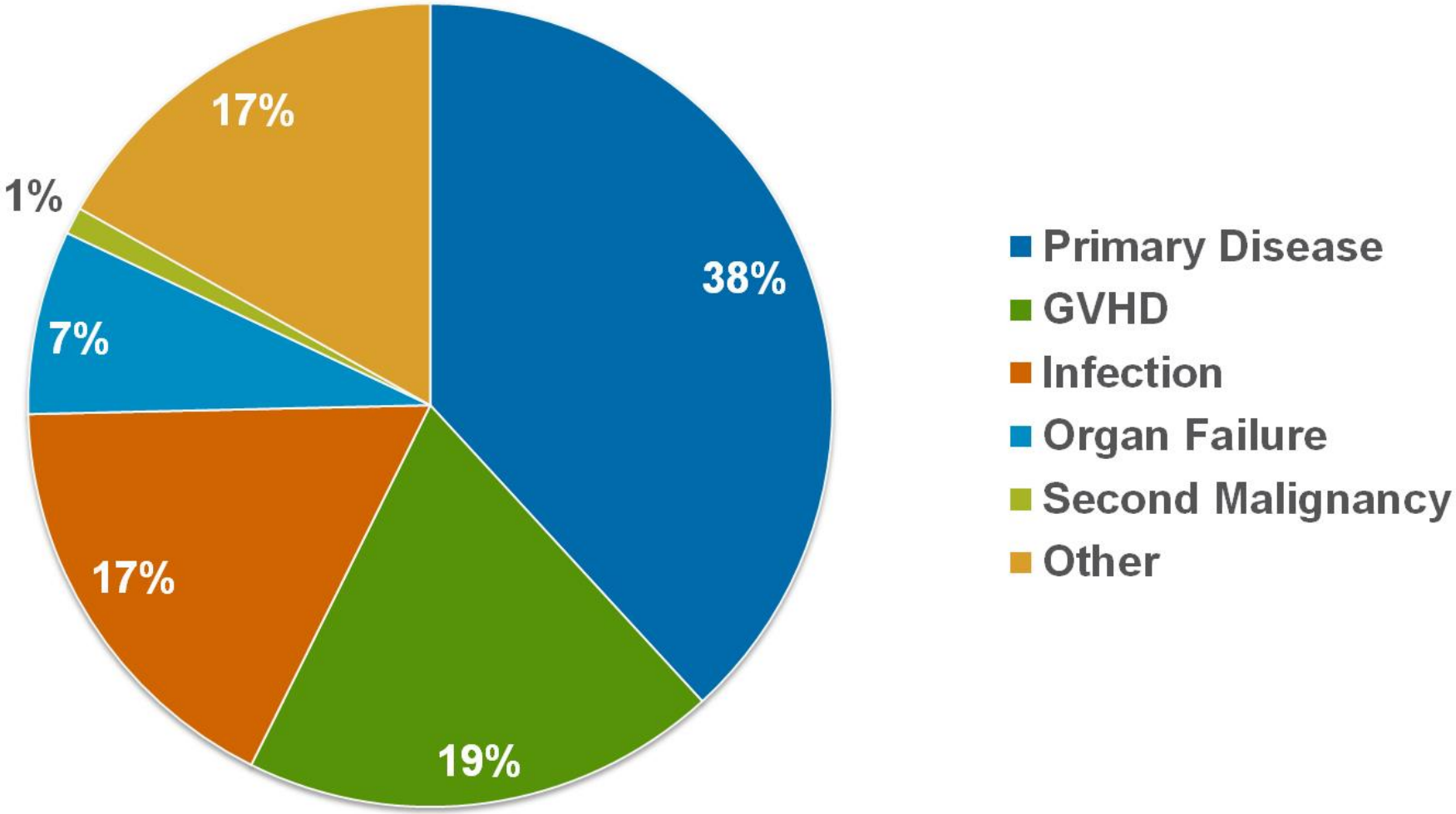
Causes of Death after Unrelated Donor Transplants done in 2010-2011



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Stem Cell Transplantation

- Allogeneic transplants have a lower rate of relapse, but more non-leukemia related deaths
- The increase in non-leukemic death is directly or indirectly (due to infection) related to graft-versus-host disease

Graft versus Host Disease

- Complex interaction between donor and recipient cells
  - Good - destroys cancer cells
  - Bad - damages normal tissues
    - Skin
    - Lungs
    - Gastrointestional tract

Graft versus Host Disease

- Classification of Graft versus host disease (GVHD):
  - Acute- mediated by T cells only
    - Occurs in the first 60 days post-transplant
  - Chronic- involves multiple cell types
    - Occurs more than 60 days post-transplant

Graft versus Host Disease

- Standard approach for prophylaxis combines:
  - drugs that block IL-2 (a growth factor for T cells)
    - Cyclosporine A
    - Tacrolimus
    - Sirolimus
  - anti-metabolites
    - methotrexate
    - mycophenolate

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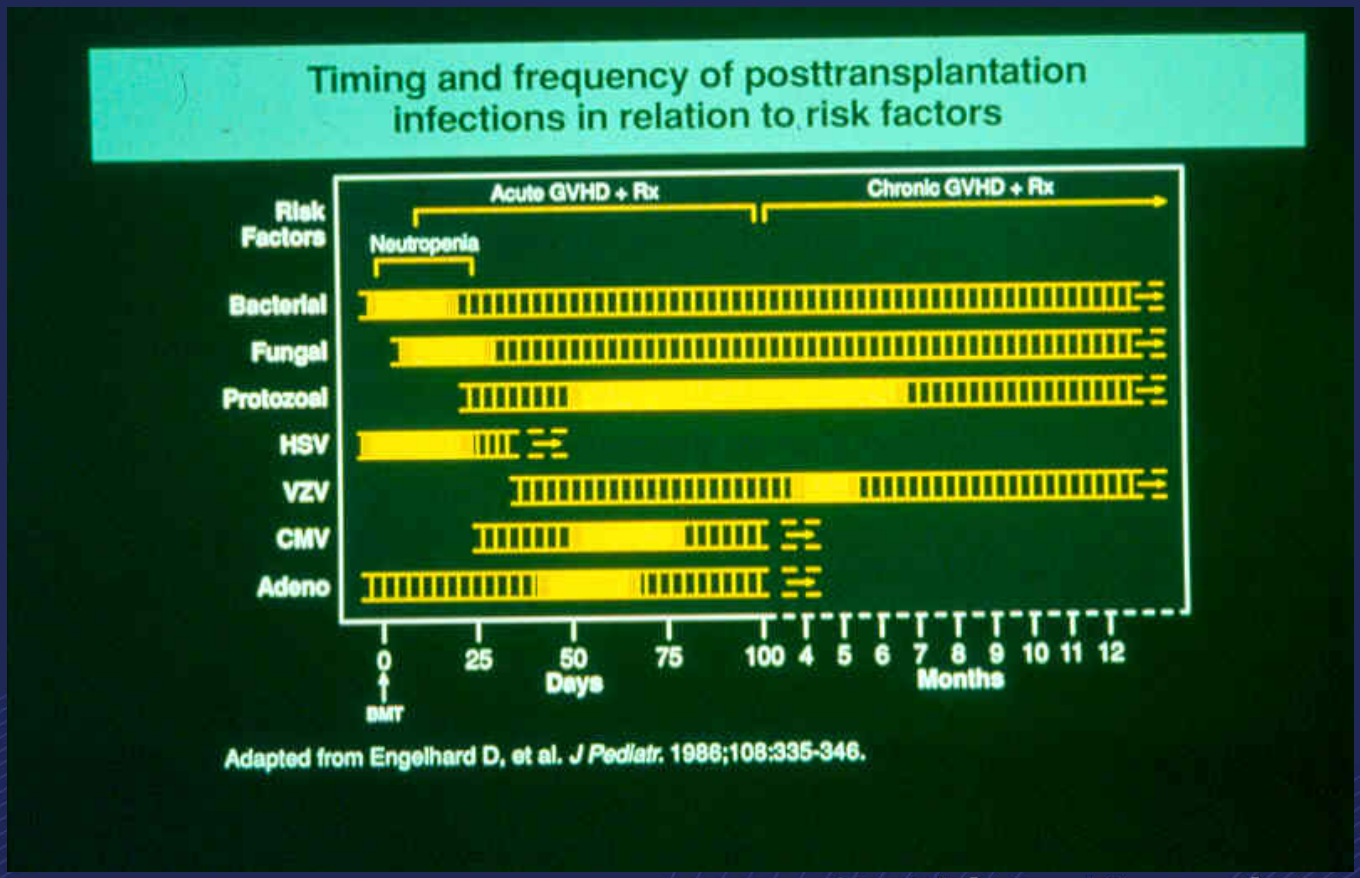
Graft versus Host Disease

- Treatment of acute GVHD
  - Corticosteroids ± anti-IL-2 therapy
  - predictors of outcome include:
    - severity
    - response to treatment at 14 days
    - HLA disparity
    - LFT abnormalities
  - best salvage therapy remains unknown
    - Photopherisis?

Impact of Graft-vs-Host Disease on Infectious complications after allogeneic transplants



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Stem Cell Transplantation

- Fungal infections are particularly dangerous to patients being treated for graft-vs-host disease
- Related to the drugs used to treat the patient, especially corticosteroids
- Half the patients have normal white blood counts at diagnosis

Stem Cell Transplantation

- The best way to deal with infection is to prevent it
- Patients routinely receive prophylaxis to prevent certain infections including:
  - Herpes virus infections (acyclovir)
  - Pneumocystis carinii pneumonia (bactrim, dapsone, atovaquone)
  - Encapsulated bacteria (bactrim, penicillin)
  - Other bacteria usually not a problem after counts recover

Factors that Increase Risk of Infection

- ANC <100
- Prolonged duration of neutropenia
- Impaired phagocyte function
- Decreased cellular and/or humoral immunity
- Alterations of anatomic barriers e.g.
  - Mucositis
  - IV catheters

Autologous Stem Cell Transplantation

- FEVER may be only indicator of infection
- Untreated infection, especially if caused by gram-negative bacilli, may be fatal
- Empiric antibiotics must be instituted ASAP (ideally within 1 hr)

Autologous Stem Cell Transplantation

- Empiric regimen should cover both gm+ and gm- organisms, including *Pseudomonas aeruginosa*
  - patient with severe sepsis: add vancomycin and tobramycin pending cultures
- Microbiologic diagnosis is made in less than 50% of patients

Typhilitis

- Invasive infection of cecum with bowel flora
  - Patients usually look ill
  - RLQ pain, heme+ stool
  - Polymicrobial bacteremia
  - Test of choice is abdominal CT

Typhilitis - Treatment

- Broad spectrum antibiotics, inc. anaerobic coverage
- Bowel rest

Antifungal Therapy in Neutropenic Transplant Recipients

- Start empiric antifungal therapy for persistent fever on broad spectrum antibiotics
- Risk of fungal infection increases with DURATION of neutropenia
- Fungal infections, especially due to molds, are difficult to diagnose early

Candida Bloodstream Infections

- 5-10% of all nosocomial bloodstream infections (BSI)
- 4th most common cause of BSI
- Associated with 40% overall mortality

Risk Factors for Candidemia

- Neutropenia
- Central venous catheters
- Total parenteral nutrition
- Broad spectrum antibiotics
- Renal failure
- Abdominal surgical procedures

Diagnosis of Disseminated Candidiasis

- Bactec cultures typically take 2 to 4 days
- Fungal blood cultures (Isolator tube) are SLOWER – do NOT order routinely
- 15% of patients will have negative blood cultures

Treatment of *C. albicans*

- Fluconazole is drug of choice
- For fungemia, give fluconazole 800 mg loading dose; then 400 mg qday (IV/po)
- Prolonged exposure can lead to colonization with fluconazole resistant candida
- If species not yet identified and pt is unstable, use Amphotericin or Echinocandin

Invasive Mold Infections

- Very difficult to diagnose early
- Pulmonary aspergillosis is most common infection
  - Unexplained fever
  - Cough, pleuritic chest pain, hemoptysis
- Invasive sinusitis

Risk Factors for Invasive Mold Infections

- Prolonged neutropenia
- Bone marrow transplant
  - Risk increases with graft vs. host disease
- Solid organ transplant
  - Lung, liver, pancreas > heart, kidney
- High-dose corticosteroid therapy

Aspergillus

- Diagnosis
  - Tissue biopsy for pathology and culture
- Treatment
  - Early treatment is critical
  - Voriconazole is drug of choice
    - Amphotericin, Micafungin are alternatives
  - Role of surgical resection

Galactomannan Assay for Aspergillus (serum)

- Limited sensitivity
- Recent study suggests ↑ sensitivity in BAL fluid (Meersseman et al. Am J Respir Crit Care Med 2008: 177;27)
- Sensitivity ↓ by concomitant antifungal rx
- False positives:
  - Zosyn, Unasyn
  - Other fungal infections

Other Noninvasive tests

- Beta-D-Glucan test
  - Detect wide range of fungi (not specific for Aspergillus)
- PCR
- Both have limited sensitivity

Voriconazole

- Wide distribution in tissues inc. CNS
- Transient visual changes common
- Excellent oral bioavailability but should check trough levels*
  - Low trough levels assoc. with rx failure
  - Hi trough levels assoc. with encephalopathy
  - Monitor for hepatitis

*Pasqual et al., CID 2008: 46;201.

Voriconazole – Drug interactions

- Metabolized by CYP450 isoenzymes
  - CYP450 inducers e.g. rifampin, carbamazepine, barbiturates ↓ levels (contraindicated)
- Inhibits CYP3A4, CYP2CP pathways
  - ↑ levels of cisapride, sirolimus (contraindicated)
  - Omeprazole, cyclosporine, tacrolimus (reduce dose)
- 2-way interactions with phenytoin (CYP450 inducer, CYP2CP substrate)
  - Vori levels ↓
  - Phenytoin levels ↑

Echinocandins

- Inhibits synthesis of GLUCAN, an integral component of fungal cell wall
- IV formulation only
- Active vs. most yeasts
  - NOT active vs.Cryptococcus (cell wall does not contain glucan
- Active against Aspergillus species

Other Molds

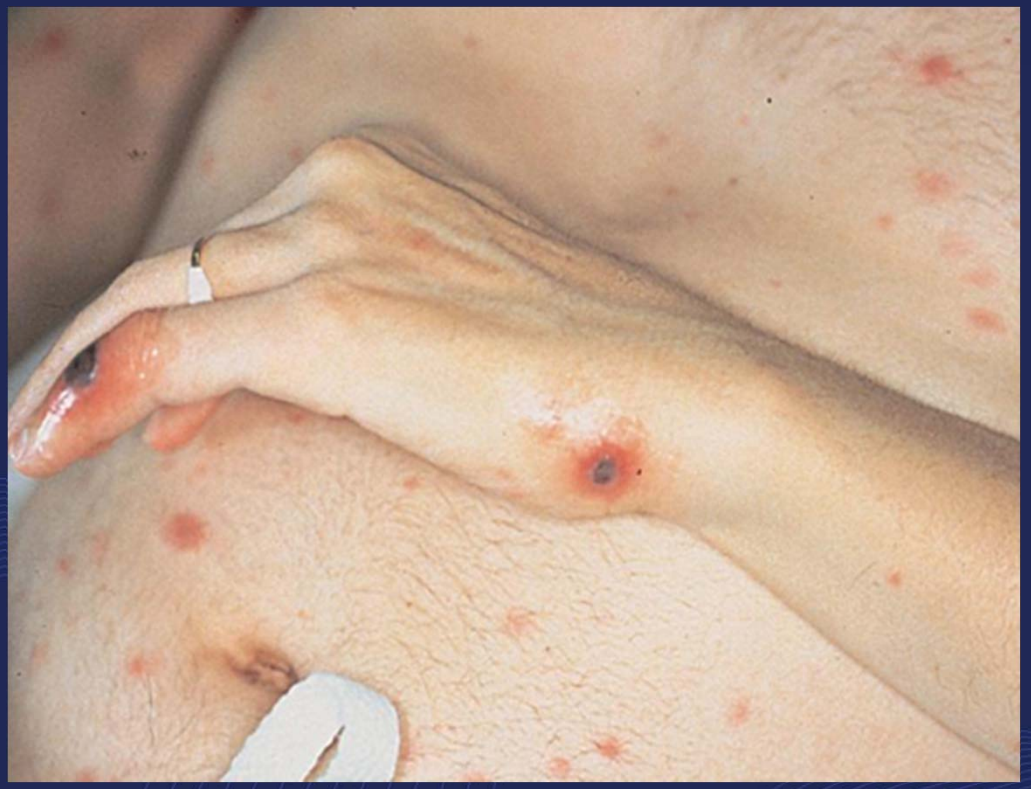
- Zygomycosis (e.g. Mucor)
  - Invasive sinus and/or pulmonary disease
  - R to voriconazole
  - Treat with high dose Ambisome, aggressive surgery

Posaconazole (Noxafil)

- First imidazole active vs Zygomycetes
- Bioavailability issues
  - Oral suspension only
  - Must administer with full meal to optimize absorption
- Drug interactions - inhibits CYP3A4
- Side effects inc. QT prolongation, hepatitis

Fusarium

- Frequently ass. with skin lesions and positive bcs
- May be susceptible to Amphotericin and Voriconazole



Summary

- For transplant pt with neutropenic fever, evaluate risk level, perform hx and exam, cultures, Xrays, and initiate broad spectrum Abx within 1-2 hrs
- In a stable pt, Abx changes or additions should be based on evidence of infection, not on persistence of fever alone
  - Exception: add empiric antifungal rx after 4-7 days
- In autologous recipients, risk diminishes rapidly as counts recover

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Infections in Allogeneic Stem Cell Transplant Recipients

- Immune dysfunction is severe and prolonged
- Infection is a major cause of morbidity and mortality
- Types of infection vary according to time interval post-transplant

Phase 1: First 30 days

- High risk of bacterial and fungal infections
  - Granulocytopenia
  - Abnormal anatomic barriers
    - ☞Chemotherapy-related mucositis
    - ☞IV catheters

Viral Pathogens (Phase 1)

- Herpes simplex virus
  - Reactivates in 20-40% w/I first year post-SCT
  - Prophylaxis during transplant and for first yr reduces risk (longer if GVHD)
- Phase II trials of irradiated VZV vaccine, recombinant protein vaccine ongoing in autologous SCT patients

Phase 2: 30 - 100 days

- Depressed cell-mediated immunity
  - High risk of viral infections, especially CMV
  - Other intracellular pathogens
- Graft vs host disease
  - Increases risk of infection

Cytomegalovirus

- Major viral pathogen in allogeneic SCT pts
- 70 -80% rate of reactivation in CMV Ab+ recipients
  - Over 1/3 develop disease
- Lower incidence of CMV infection in CMV Ab- recipients with CMV Ab+ donor

Cytomegalovirus Disease

- Fever, neutropenia, thrombocytopenia
- Interstitial pneumonia – high mortality
- Esophagitis, gastroenteritis
- Hepatitis

CMV Pneumonia

- Etiology of 1/3 of cases of interstitial pneumonia.
- Diagnosis
  - BAL for CMV culture and PCR
  - Tissue biopsy
- Treatment
  - Ganciclovir plus high-dose IV Ig for 3 weeks
  - Maintenance ganciclovir

CMV Prophylaxis

- In light of high mortality, prophylaxis or pre-emptive treatment recommended
- Positive blood CMV PCR associated with high risk of progression to active disease
  - Obtain weekly quantitative PCR
  - If positive, start ganciclovir or foscarnet
  - Monitor response by PCR

CMV Treatment Issues in SCT recipients

- In some cases, CMV viremia increases despite antiviral rx
- How to treat?
  - Reduce immunosuppression if feasible
  - Combination rx with 2 antivirals: ganciclovir and foscarnet are synergistic in vitro
  - CMV IV IgG (Cytogam)

Human Herpes Virus 6

- Lymphotropic herpes virus
  - Roseola, other febrile illness in young children
  - High seroprevalence >90%
- Frequently reactivates post-allogeneic SCT but usually self limited
  - Associated with fever, rash, and delayed platelet engraftment
  - Rarely causes encephalitis or pneumonitis
  - Susceptible to ganciclovir or foscarnet

HHV6 post-SCT

- NO routine surveillance
- Check HHV6 PCR if patient has unexplained
  - fever and rash, cytopenia, confusion/seizures, or pneumonitis
- If >25,000 copies/ml, start Foscarnet or ganciclovir
- If <25,000, assess on individual pt basis
- If PCR+ with change in mental status, perform LP and start rx pending results

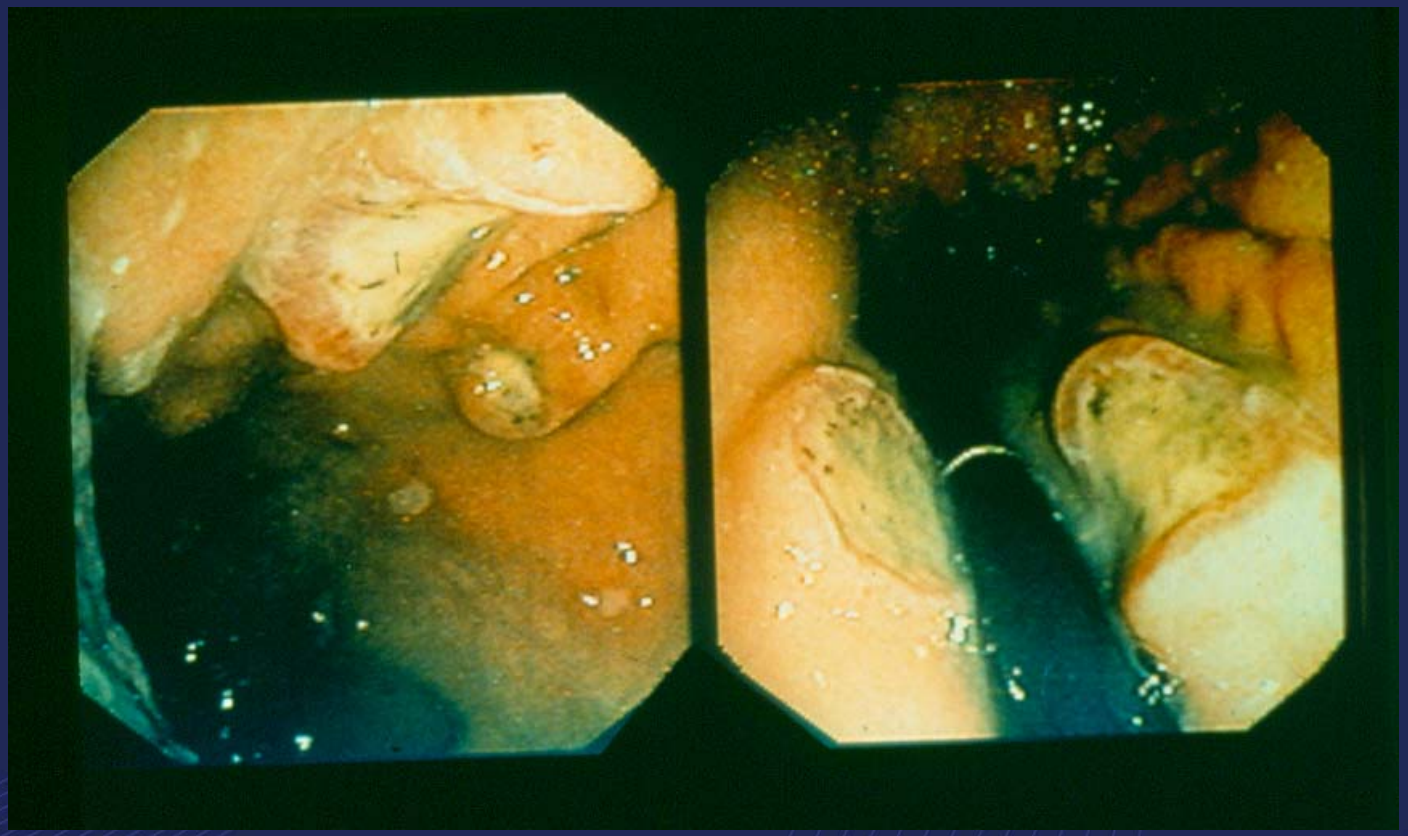
Epstein-Barr Virus-associated Lymphoproliferative Disease

- Clinical manifestations
  - Persistent fevers
  - Lymph node enlargement
  - Extranodal masses – GI tract, lung, liver, CNS
- Diagnosis
  - Tissue bx - monoclonal B cell proliferation
  - EBV blood PCR: rising levels ass. with ↑ risk

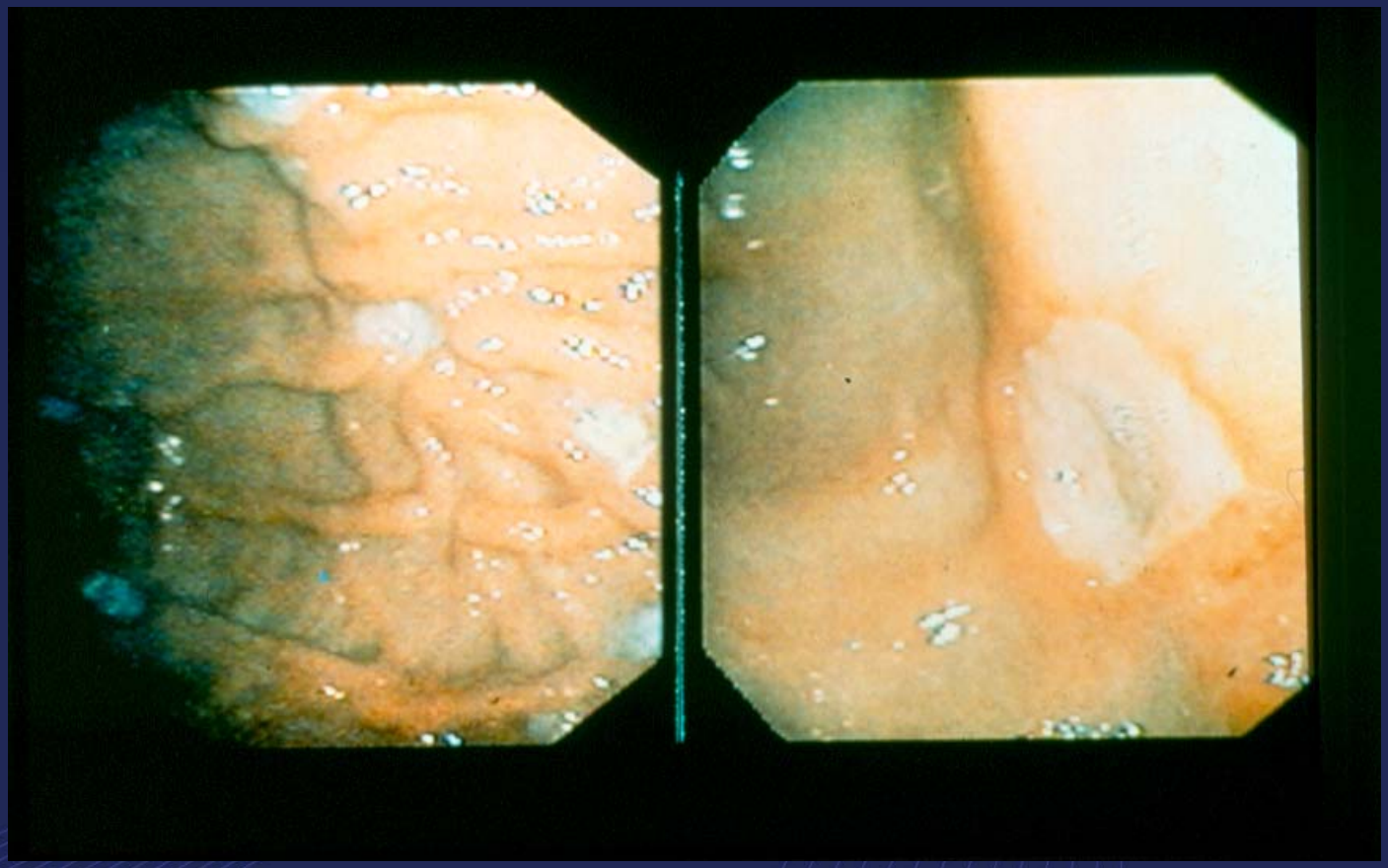
Treatment of PTLD

- Reduce immunosuppression
- anti-CD20 monoclonal antibody (vs. B cells)
- Donor lymphocyte infusions

Allogeneic Stem Cell Transplantation



Allogeneic Stem Cell Transplantation



BK virus

- Papillomavirus virus frequently reactivates post allo SCT – approx 50% of patients
- Commonly ass. w hemorrhagic cystitis
  - 10-25% of patients
- Usually localized disease but sx can be severe and prolonged
  - Uncommonly causes ureteral stenosis
  - Renal involvement is rare (unlike renal TX)

BKV management

- Supportive rx e.g. IV fluids, bladder irrigation
- Most effective intervention is to reduce immunosuppression
- Cidofovir
  - Active vs BKV but efficacy unclear post SCT
  - Study of 18 pts with BK cystitis; 12 had viremia*
    - 13 (72%) responded to treatment with low dose IV cidofovir (w/o probenicid) +/- intravesical cidofovir

*Ganguly et al. Transpl Infect Dis 2010:12:406

BKV management

- Leflunomide
  - Antimetabolite with antiviral and immunosuppressive activities
  - Can cause myelosuppression and liver toxicity
  - Some data for benefit in renal TX recipients
- Ciprofloxacin
  - Inhibits BKV replication by direct inhibition of BKV-encoded DNA gyrase
  - One study of cipro prophylaxis documented significant reduction in severe cystitis post-SCT*

*Miller et al. Biol Blood Marrow Transplant 2011;17:1176

BKV Treatment Algorithm

- Symptomatic viruria w/o viremia
  - Intravesical cidofovir weekly + oral cipro
  - Cont. until sx resolve and min. 1-log reduction in viruria
- Symptomatic viruria with viremia
  - IV cidofovir 0.5mg/kg weekly + cipro
  - Cont. rx until blood BK PCR neg

*Ganguly et al. Transpl Infect Dis 2010:12:406

Respiratory Viruses

- Respiratory syncytial virus
  - Outbreaks described in BMT units
  - Mortality high
  - Ribavirin may be of benefit
- Influenza
  - Antiviral prophylaxis and rx
- Parainfluenza

Adenovirus Disease

- Primary infection or reactivation of latent infection
- Clinical manifestations inc.
  - Colitis, hepatitis
  - Hemorrhagic cystitis, nephritis
  - Pneumonia, encephalitis
- Cidofovir is active but early rx critical

Human Metapneumovirus

- Recently identified paramyxovirus (RNA)
- Detected by PCR only
- Primarily causes self-limited URIs
- In SCT patients with PNA, frequently co-detected with other pathogens

Summary

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