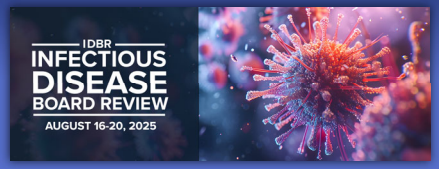


# Infections in Hematopoietic Cell Transplant Recipients

**Jennifer Saullo, MD, PharmD, FIDSA**
Associate Professor of Medicine
Transplant Infectious Diseases
Duke University Medical Center
Durham, NC

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## Disclosures of Financial Relationships with Relevant Commercial Interests

- Chapter author – UpToDate

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## Objectives

- Review fundamental concepts of hematopoietic cell transplantation (HCT)
- Review of common infectious complications in HCT
  - Relevance of transplant variables, risks and timeline
  - Differentiation of non-infectious mimics
  - Primary and secondary prophylaxis + recognition of breakthrough infections

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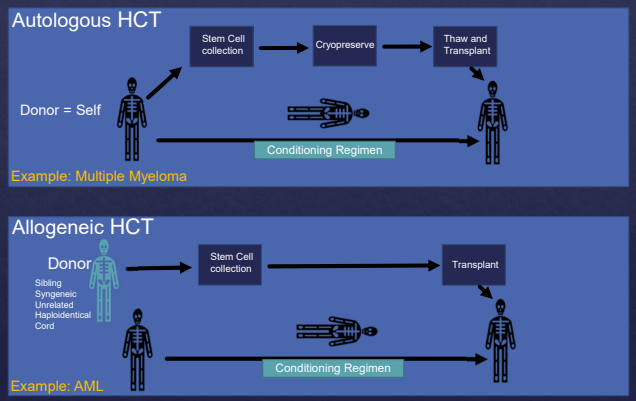
## Fundamental Concepts

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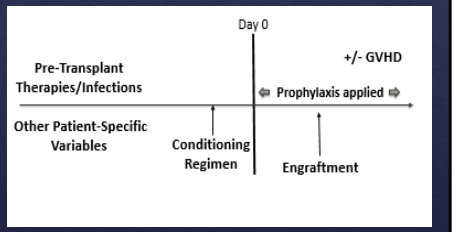
# Fundamental Concepts

## *Transplant Variables and Infection Risk*

- Transplant type
  - Autologous vs Allogeneic
- Underlying disease
- Donor/recipient age
- HLA matching
  - MRD, MUD, MMRD and UCD
- Conditioning regimen
  - Myeloablative, non-myeloablative and reduced intensity
- Source of stem cells
  - Bone marrow, peripheral blood, cord blood
- Graft manipulation
- Graft versus host disease




Matched-related donor, MRD; Matched-unrelated donor, MUD; Mismatched-related donor, MMRD; UCD, umbilical cord donor; GVD, graft versus host disease.CD

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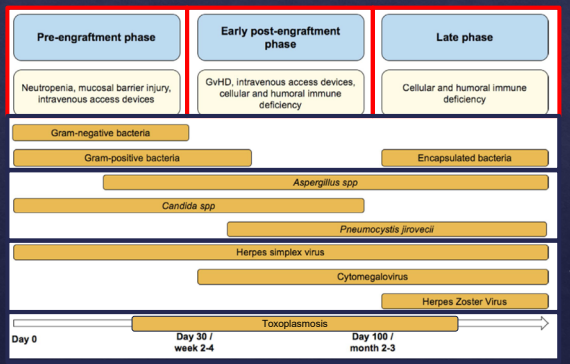
# Fundamental Concepts

## *Transplant Timeline*




Adapted from: Akhmedov M. Clin Transplant. 2021;35(2):e14172.

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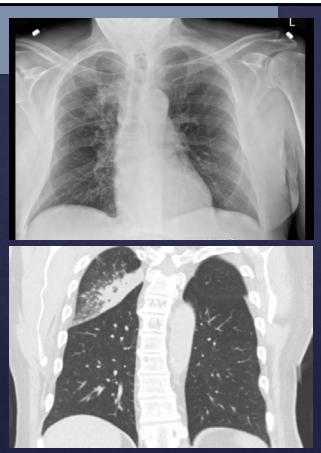
# Question #1

42-year-old male, d+20 following a matched unrelated donor (MUD), non-myeloablative (NMA) HCT develops fevers, cough and a new pulmonary infiltrate.

- Pre-transplant serologies: CMV D+/R-, Toxo D-/R-; recipient otherwise HSV/VZV+
- Exam: T 38.3, BP 120/70, HR 115, SaO2 98% on 1L, rhonchi on R
- Labs: Cr 1.5, ANC 1200/µL, platelets 43. Current prophylaxis includes acyclovir and fluconazole.



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# Question #1

**What is the most likely etiology of his current process?**

A. *Candida albicans*
B. *Pseudomonas aeruginosa*
C. Cytomegalovirus
D. Parainfluenza virus
E. Hemorrhage

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## Pulmonary Complications
### *Hematopoietic Cell Transplant*

- Key elements of the question stem
  - Timing post transplant
  - Applied prophylaxis
  - Donor/recipient serologies
- Differential
  - Infection (bacterial, fungal, viral, parasitic)
  - Non-infectious "mimics"

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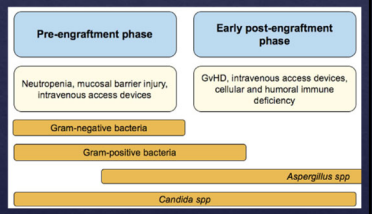
## Pulmonary Complications
### *Infections*

- Bacterial pathogens
  - *E. coli, P. aeruginosa, S. pneumoniae, S. aureus, K. pneumoniae*
  - Aspiration events, particularly with mucositis
- Fungal infections
  - *Aspergillus* most common (early & late post-transplant)
  - PJP – uncommon early, typically late + consider lapses in prophylaxis, suboptimal regimens

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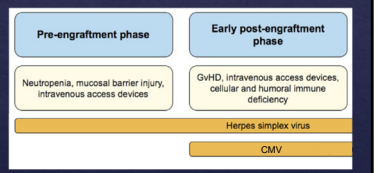
## Pulmonary Complications
### *Infections*

- Viral pathogens
  - Community acquired respiratory viruses
    - Influenza, Parainfluenza, RSV, Human metapneumovirus, Adenovirus, Rhinovirus, SARS-CoV-2
    - Increased risk for lower respiratory tract involvement
  - Herpesvirus
    - CMV >> HSV/VZV
    - CMV typically occurs post-engraftment, onset further delayed with primary CMV prophylaxis
- Other (Toxoplasmosis, Strongyloidiasis)

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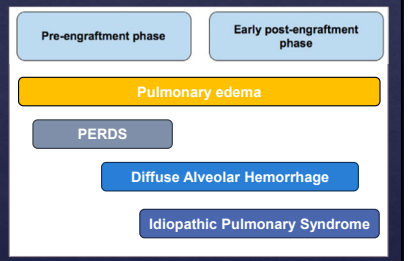
## Pulmonary Complications
### *Non-infectious*

- Early non-infectious considerations
  - **Pulmonary edema**
  - **Engraftment syndrome / PERDS**
    - Fever, rash, diffuse pulmonary opacities
  - **Diffuse alveolar hemorrhage**
    - Heterogenous etiology – infection, GVHD, alveolar injury
    - Progressively hemorrhagic return on bronchoalveolar lavage
  - **Idiopathic pulmonary syndrome**
    - Dry cough, hypoxia, diffuse infiltrates




Peri-engraftment respiratory distress syndrome, PERDS.

Adapted from: Astashchanka A et al. J Clin Med. 2021;10(15):3227.

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## Question #2

PREVIEW QUESTION

A 46-year-old male **18 months** s/p HLA mismatched allogeneic HCT

- HCT course complicated by GVHD involving the skin, GI tract, and lungs. Treated with steroids 3 months ago
- One month ago, he had Parainfluenza 3 with chest CT demonstrating tree-in-bud opacities in LLL. Received levofloxacin for 10 days
- Now presents with increasing shortness of breath and cough

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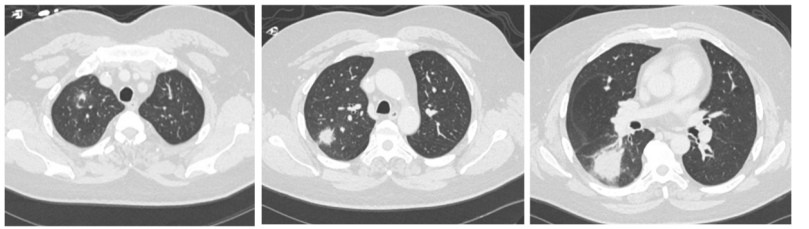
## Question #2

PREVIEW QUESTION

Different cuts on same CT



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## Question #2

PREVIEW QUESTION

Blood cultures are negative. Sputum cultures grow oropharyngeal flora. Serum galactomannan is negative.

**What is the <u>most likely</u> etiology of his current process?**

A. *Cryptococcus neoformans*
B. *Escherichia coli*
C. *Staphylococcus aureus*
D. *Aspergillus fumigatus*
E. *Fusarium* spp.

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## Invasive Aspergillosis in HCT

- Most common invasive mold (allogeneic > autologous HCT)
- Pulmonary involvement (IPA) predominates
- Look for specific risks in the question stem
- Bi-modal distribution (d<100, d+180)
- Primary prevention
  - High risk allogeneic HCT- mold-active prophylaxis through at least d +75
  - GVHD (posaconazole A-I; alternative is voriconazole (B-I), isavuconazole also utilized)
- Diagnostic pearls - negative aspergillus GM does NOT exclude IA if on mold-active prophylaxis or non-neutropenic
- Treatment – generally a minimum of 3 months, radiographic resolution + clinical improvement

| Risks for Invasive Aspergillosis |
|---|
| Pre-transplant IA |
| Specific comorbidities – hematologic malignancy, diabetes, Fe overload |
| Prolonged neutropenia |
| GVHD |
| Community acquired respiratory viral infections; CMV reactivation |
| Environmental exposures (construction, gardening, marijuana) |

Dadwal SS et al. Transplant Cell Ther. 2021;27(3):201.

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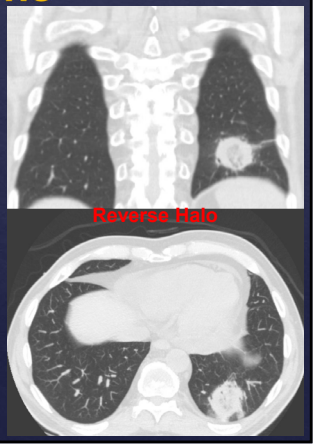
## Pulmonary Complications
### *Late/Post Engraftment +*

- Infectious
  - Fungal - *Aspergillus*, PJP, other molds
  - Bacterial (encapsulated, *Nocardia)*, Mycobacteria
  - Respiratory viruses, CMV
- Non-infectious
  - Organizing pneumonia
  - Bronchiolitis obliterans syndrome

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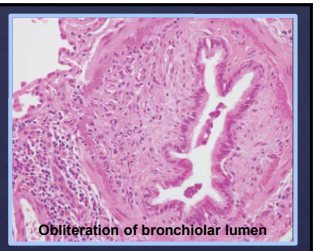
## Pulmonary Complications
### *Bronchiolitis Obliterans*

- Chronic GVHD of the lungs
- Inflammatory and fibroproliferative process focused on the terminal bronchioles
- Clinical presentation - cough, increasing shortness of breath and dyspnea on exertion
- Diagnostics
  - PFTs: narrowing of the bronchiolar lumen → airflow obstruction
  - CT imaging: air trapping, "mosaicism"




From: Williams KM et al. JAMA 2009;302(3):306.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## Question #3

50-year-old female with refractory AML is set to receive a matched unrelated donor allogeneic HCT with fludarabine/busulfan and post-transplant cyclophosphamide. CMV serostatus of the donor and recipient is positive.

**What is the most appropriate preventative approach?**

A. Pre-emptive therapy with letermovir
B. Primary prophylaxis with letermovir
C. Primary prophylaxis with (val)ganciclovir
D. Primary prophylaxis with foscarnet
E. None of the above, the patient is not at risk for CMV infection

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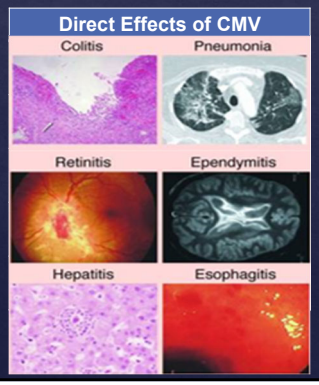
## CMV Infection in HCT
### *The "Troll of Transplant"*




| Indirect Effects of CMV |
|---|
| Bacteremia |
| Graft versus host disease |
| Invasive fungal infections |
| Non-relapse mortality |

- Figure left, adapted from: Boeckh M, Geballe AP. J Clin Invest 2011;121:1673,
- Hakki M et al. Transplant Cell Ther. 2021;27(9):707.

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## CMV Infection in HCT
### *The "Troll of Transplant"*

| Risks for CMV in HCT |
|---|
| **CMV Seropositive recipient (R+ >>> D+/R- >> D-/R-)** |
| Graft versus host disease and applied therapies (e.g. prednisone > 1 mg/kg/day equivalent) |
| T-cell depletion (e.g. alemtuzumab, ATG) |
| Cord blood transplant |
| Haploidentical, mismatched or unrelated donors |
| Lymphopenia |
| Older age |

Hakki M et al. Transplant Cell Ther. 2021;27(9):707.

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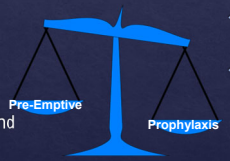
## CMV Infection in HCT
### *Prevention[1]*

**Pre-Emptive**

- Weekly CMV DNA PCR monitoring through at least day +100
- CMV DNAemia > threshold = initiation of antiviral
  - Typical therapy – (val)ganciclovir >> foscarnet
  - Induction dosing ~ 2 weeks and until DNAemia clearance




**Primary Prophylaxis**

- Initiated by day +28 through at least day +100 in highest risk (R+)[2]
- Extension through day +200 can be considered high risk patients[3]
- Letermovir (FDA-approved)
  - Lacks side effects - cytopenias and nephrotoxicity
  - Lacks activity against HSV/VZV
  - Relevant DDI (azoles - vori, calcineurin inhibitors)

1. Hakki M et al. Transplant Cell Ther. 2021;27(9):707.
2. Marty FM et al. N Engl J Med. 2017; 21;377(25):2433.
3. Russo D et al. Lancet Haematol. 2024;11(2):e127.

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## CMV Infection in HCT
### *Refractory / Resistant CMV*

**Refractory CMV Infection**

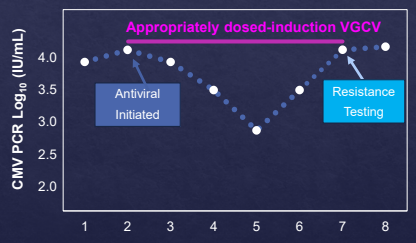
CMV viremia that increases (ie, >1 log10) OR persists (ie, ≤1 log10 increase or decrease) after at least 2 weeks of appropriate antiviral therapy

**Refractory CMV End-Organ Disease**

Worsening signs and symptoms or progression to end-organ disease OR lack of improvement after at least 2 weeks of appropriately dosed antiviral therapy

**Resistant CMV Infection**

Refractory CMV infection AND viral genetic alteration decreasing susceptibility to 1 or more antiviral drugs




Ljungman P, et al. *Clin Infect Dis.* 2024;26;79(3):787.

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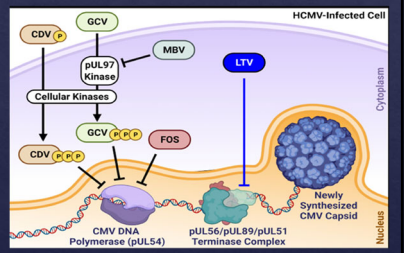
## CMV Infection in HCT
### *Treatment of Infection +/- Resistant / Refractory CMV*

- Induction therapy typically with (val)ganciclovir
- Resistance to (val)ganciclovir is rare (*compared to SOT*)
  - Most failures due to profound immunocompromise – e.g. steroids, other T cell depletion
  - Clues for resistance - long exposure to suboptimal doses, poor cellular immunity
  - Resistant and refractory disease
    - Foscarnet, Maribavir
    - Letermovir is for CMV prevention NOT treatment




CDV, cidofovir; CMV, cytomegalovirus; FOS, foscarnet; GCV, ganciclovir; LTV, letermovir; MBV, maribavir.

Figure from: Saullo JL, Miller RA. Annu Rev Med. 2023;74:89.

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## *Pneumocystis jirovecii* in HCT

- Allogeneic >> Autologous
  - Shift with routine prophylaxis – now a late complication
  - Risks – steroids, T-cell depletion
- Prophylaxis applied at least 6 months post-transplant
  - Primary – sulfamethoxazole-trimethoprim (SMX-TMP)
  - Non SMX-TMP alternatives *(less effective, potential for breakthrough)*
    - Atovaquone
    - Dapsone
    - Aerosolized pentamidine
- Tropism for lungs, rare disseminated infection
- Radiograph findings – "any and none", most commonly diffuse radiographic infiltrates

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## Toxoplasmosis in HCT

- Seroprevalence higher in in NE US (30%), foreign born (25-50%)
- Risk in allogeneic HCT >>> autologous HCT
- 90% of cases within the first 6 months post-HCT
  - Most occur between post-transplant months 2 thru 4
  - Over 2/3 represent reactivation in seropositive recipients
- Presentation with fever, pneumonia, encephalitis *(recognize the lack of prophylaxis in the question stem)*
- Uncommon but deadly - high mortality, diagnosis often delayed

Gajurel K et al. Curr Opin Infect Dis. 2015;28(4):283.

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## Question #4

PREVIEW QUESTION


35-year-old female, d+80 after allogeneic HCT presenting with **5 days of anorexia, nausea, epigastric pain, and diarrhea**. CMV D-/R+, HSV+, VZV+.

- Exam: **faint maculopapular rash** on upper body. Afebrile.
- **Antimicrobials: acyclovir, letermovir, TMP-SMX and fluconazole.**
- Labs: ANC 1200, ALC 250. Hepatic panel within normal limits. Stool PCR for norovirus and *C. difficile* negative. Plasma quantitative CMV PCR negative.

**What is the most appropriate initial work-up and management?**

A. Perform serum varicella zoster virus (VZV) PCR
B. Empiric corticosteroid treatment
C. Blood lipase and amylase
D. Upper and lower endoscopy

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## Graft Versus Host Disease

- Immune cells from the donor graft recognize host cells as "foreign"
- 3 forms exist: acute, chronic and GVHD overlap (NIH consensus criteria)
- Acute – typically early post transplant
  - Rash +/- fever
  - GI manifestations (nausea, vomiting, anorexia, diarrhea), acute hepatitis
- Chronic – typically later post transplant
  - Can affect virtually any organ
    - Skin - lichen planus, scleroderma-like
    - Liver - hepatitis, cholestatic picture
    - GI tract - nausea, vomiting, chronic diarrhea, weight loss
    - Lungs - bronchiolitis obliterans syndrome
    - Eyes - dry, painful eyes

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## GVHD in HCT

***GI manifestations (infection mimic)***

**Hepatitis**

- GVHD
- Herpesviruses (CMV, VZV, HSV)
- Other viral hepatitis
  - Hepatitis B (less common A/C/E)
  - Adenovirus

**Diarrhea**

- GVHD
- CMV
- *C. difficile*
- Norovirus (chronic diarrhea)
- Adenovirus

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## Question #5

40-year-old male, d+60 following allogeneic HCT from a MUD presents with bloody urine for 6 days. Also has skin GVHD with recent initiation of high-dose prednisone (1 mg/kg/day) with ongoing taper.

- Exam demonstrates a faint diffuse erythematous rash.
- Cr 1.2, hepatic panel within normal limits. CMV quantitative plasma PCR is negative.

**What is the most likely etiology?**

A. Cyclophosphamide
B. Cytomegalovirus
C. Epstein-Barr virus
D. BK virus
E. HHV-6

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## Hemorrhagic Cystitis in HCT

- Early occurrence
  - Following conditioning regimen
  - Therapy-related (e.g., cyclophosphamide, busulfan)
- Later occurrence
  - Post-engraftment
  - Viral infection (e.g., BK virus, adenovirus)

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## Question #6

68-year-old male with CMML (CMV, HSV and VZV seropositive) underwent a reduced intensity allogeneic HCT with multiple complications including pneumonia, BK cystitis and acute graft versus host of the GI tract requiring recent initiation of high dose steroids. He presents with fever, lethargy, confusion and appreciable weakness.

- Head CT is non-focal but brain MRI reveals mild flair hyperintensity with diffusion restriction in the right hippocampus and parahippocampal gyrus.
- Plasma HHV6 PCR is 1600 copies/mL.

**What are the best next steps in management?**

A. Initiation of IV acyclovir for HHV-6 encephalitis, no further diagnostic work-up required
B. Initiation of IV ganciclovir for HHV-6 encephalitis, no further diagnostic work-up required
C. Initiation of empiric IV ganciclovir and pursue additional diagnostics with lumber puncture
D. Initiation of IV foscarnet for HHV-6 encephalitis, no further diagnostic work-up required
E. Initiation of empiric IV letermovir and pursue additional diagnostics with brain biopsy

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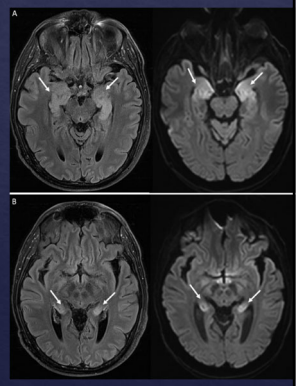
## Human Herpes Virus-6 (HHV-6)

- Ubiquitous herpesvirus, seroprevalence > 95% after age 2
- Viremia common post-allogeneic HCT (~ 40-70%)
- Clinical associations - rash, fever, myelosuppression, hepatitis, pneumonitis
- **Meningoencephalitis**** (most testable manifestation; HHV-6B)
  - Nonspecific presentation (confusion, memory loss, seizures)
  - Generally early post-transplant (before day +100), uncommon (1-3% allo HCT)
  - Risks - mismatched/unrelated donors, umbilical cord blood, T-cell depletion, GVHD and steroids
  - Diagnosis via history, MRI/EEG (temporal region), PCR of CSF
- Chromosomal integration (1%)
- Treatment: ganciclovir, foscarnet >> cidofovir (acyclovir resistant, letermovir lacks activity)




Marcelis S et al. J Belg Soc Radiol. 2022;06(1):93.

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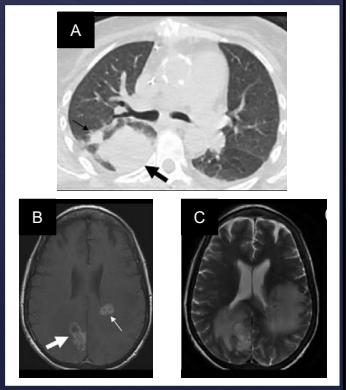
## Neurologic Syndromes in HCT

- Infection
  - Pulmonary – CNS lesions
    - Invasive fungal infections
    - *Nocardia*
    - Toxoplasmosis
  - Viral pathogens
    - Herpes viruses – HSV, VZV, CMV, **HHV-6***, EBV
    - West Nile virus
    - **JCV – PML***

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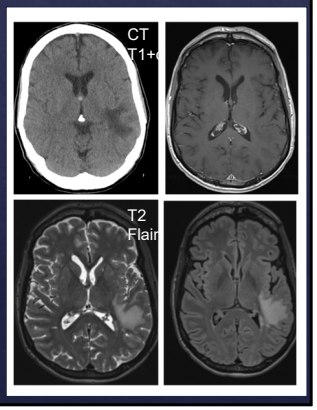
## Progressive Multifocal Leukoencephalopathy (PML)

- Demyelinating CNS infection due to reactivation of JC virus
- Rare, described in multiple populations - malignant hematology (HL, CLL), HIV, SOT/HCT, inflammatory/autoimmune disorders (including multiple sclerosis)
- Specific risks include applied immunomodulatory therapies - **monoclonal antibodies, specifically natalizumab;** others rituximab, efalizumab, eculizumab, belatacept, ibrutinib*
- Clinical presentation
  - Months to years after HCT
  - Progressive, subacute neurological deficits - cognitive impairment, limb and gait ataxia, weakness, visual changes, hemiparesis, aphasia
- Diagnostics - CNS imaging (*asymmetry, periventricular/subcortical, non-contrast enhancing, spares grey matter), CSF PCR, brain biopsy
- Treatment - no effective treatment; immune restoration key

*list not all-inclusive

  - PRES also tends to have more gray matter involvement and does not cause hypointense lesions on T1-weighted magnetic resonance imaging (MRI). (See "Reversible posterior leukoencephalopathy syndrome".)

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## Neurologic Syndromes in HCT

- Infection
  - Viral pathogens
    - Herpes viruses
    - West Nile virus
    - JCV
  - Pulmonary – CNS lesions
    - Invasive fungal infections
    - *Nocardia*
    - Toxoplasmosis
- Non-Infectious
  - Antibiotics – carbapenems, cefepime
  - Posterior reversible encephalopathy syndrome (PRES)

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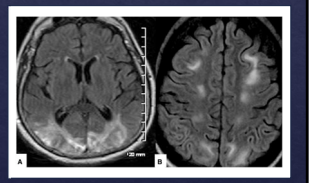
## Posterior Reversible Encephalopathy Syndrome (PRES)

- Aka reversible posterior leukoencephalopathy syndrome (RPLS)
- Uncommon overall in HCT (<10%)
- Risks / conditions include hypertension, renal disease, autoimmune disorders and applied immunosuppressive / immunomodulatory therapies (CNI, cyclophosphamide)
- Clinical presentation – acute to sub-acute, altered consciousness, headaches, visual disturbances, seizures
- Diagnostics – neuroimaging (CT/MRI)
  - Cortical and subcortical involvement (image A)
  - Bilateral vasogenic edema in occipital and parietal regions +/- watershed areas (image B)
- Treatment – supportive, reversal of associated culprit +/- antiseizure medications



From: Shankar J, Banfield J. Can Assoc Radiol J. 2017;68(2):147

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## Other Viral Infections in HCT

### *HSV/VZV**

**Herpes Simplex Virus (HSV)**

- Risk generally greatest early post-transplant
- Clinical presentation
  - Mucositis /esophagitis most common
  - Visceral, neurologic and ocular less common
- Resistance emergence (acyclovir/valacyclovir)
  - Uncommon (3.5-10%)
  - Mechanism: altered thymidine kinase *(UL23 mutation)* >>> altered DNA polymerase *(UL30 mutation)*

**Varicella Zoster Virus (VZV)**

- Risk generally late post-transplant
- Clinical presentation
  - Cutaneous most common
  - Visceral (pneumonitis, hepatitis), neurologic and ocular less common
    - Can occur without skin lesions *(consider in case of severe abdominal pain, transaminitis & without rash)*
- Resistance rare

*Think about "holes" in prophylaxis, breakthrough/resistance

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## Pearls

- Fundamentals – Risks (temporality, prophylaxis)
  - Early – mucositis, neutropenia
  - Late – GVHD (steroids, asplenia, T cell dysfunction and other delays in IRC)
- Syndromes
  - Early pulmonary syndromes
    - Bacterial, fungal pneumonia
    - Non-infectious: Alveolar hemorrhage, IPS, engraftment
  - Late pulmonary syndromes
    - CMV, respiratory viruses, fungal infections
    - Non-infectious: BO, organizing pneumonia
- Hemorrhagic cystitis
  - BK >> adenovirus
  - Non-infectious: conditioning
- Diarrhea – colitis – hepatitis
  - Herpesviruses
  - Non-infectious: GVHD
- Neurologic syndromes
  - Herpesviruses (+HHV-6), west nile, angioinvasive molds, toxoplasmosis
  - PML
  - Non-infectious: PRES, antibiotics

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## Thank You

Questions/Comments:

jennifer.horan@duke.edu

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## Additional References

- Vaccinations and HCT
  - Carpenter PA, Englund JA. How I vaccinate blood and marrow transplant recipients. Blood. 2016 Jun 9;127(23):2824-32.
  - Pergam SA, Englund JA, Kamboj M, Gans HA, Young JH, Hill JA, Savani B, Chemaly RF, Dadwal SS, Storek J, Duchin J, Carpenter PA. Preventing Measles in Immunosuppressed Cancer and Hematopoietic Cell Transplantation Patients: A Position Statement by the American Society for Transplantation and Cellular Therapy. Biol Blood Marrow Transplant. 2019 Nov;25(11):e321-e330.