16 – Infections in the Neutropenic Cancer Patient and Hematopoietic Stem Cell Recipients

Speaker: Jennifer Saullo, MD

Infections In Neutropenic Cancer Patients and Hematopoietic Cell Transplant Recipient

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Disclosures of Financial Relationships with Relevant Commercial Interests

- None

Objectives

- Review testable complications in relevant immunocompromised hosts
- Broadly categorized, this includes
  - Risks of underlying diseases and applied chemo-, immunomodulatory and cellular therapies
  - Recognition of breakthrough infections
  - Recognition of specific clinical "syndromes"

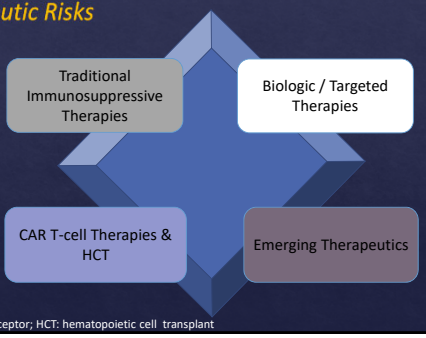
Fundamental Concepts

Risk of Underlying Disease

- Important immune deficits associated with underlying disease
- Examples include
  - Acute myelogenous leukemia (AML) and myelodysplastic syndromes (MDS) – *qualitative and quantitative neutropenia*
  - Lymphomas – *functional asplenia*
  - Chronic lymphocytic leukemia (CLL) – *hypogammaglobulinemia, complement deficiencies, neutrophil/monocyte defects*
  - Multiple myeloma – *hypogammaglobulinemia*
  - Aplastic anemia – *severe, prolonged neutropenia*

Fundamental Concepts

Therapeutic Risks



CAR: Chimeric Antigen Receptor; HCT: hematopoietic cell transplant

Fundamental Concepts

Therapeutic Risks

- Drugs that impact neutrophils
  - Cytotoxic chemotherapy (e.g. anthracycline, cyclophosphamide)
    - Infectious risks greatest when prolonged (> 7 days) and profound (< 500 cells/mm^3) neutropenia
    - Severe bacterial and fungal infections

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Fundamental Concepts
Therapeutic Risks

- Drugs that impact T cells
  - Purine analogs (fludaribine, cladribine, clofarabine) and temozolomide
    - Infections associated with
      - Herpesviruses (e.g. CMV, HSV, VZV)
      - Intracellular and other less common bacteria (e.g. Mycobacteria, *Nocardia*)
      - Fungi (e.g. PJP, *Aspergillus*)

CMV: Cytomegalovirus, HSV: herpes simplex virus; VZV: varicella zoster virus; PJP: *Pneumocystis jirovecii* pneumonia

Biologic / Targeted Therapies
Monoclonal Antibodies

Case #1: 68 year old man, originally from Taiwan, underlying follicular lymphoma with plans to initiate single-agent **rituximab** therapy.

Which of the baseline serologies would be **most important** when assessing infectious risks and relevant need for prophylaxis with rituximab therapy?

A. Cytomegalovirus
B. Toxoplasmosis
C. Hepatitis A
D. Hepatitis B ←
E. Hepatitis C

Biologic / Targeted Therapies
Monoclonal Antibodies

- RITUXIMAB – an anti-CD20 (B-cell) monoclonal antibody
  - *Others: ofatumumab, obinutuzumab*
- Results in prolonged B-cell depletion, hypogammaglobulinemia and neutropenia
- Appreciably impairs **response to vaccinations**
- Other notable infectious risks
  - **Hepatitis B viral (HBV) reactivation** - greatest risk in HBsAg+ (high) and HBcAb+ (moderate)
    - Baseline HBV testing recommended before immunosuppressive, cytotoxic, or immunomodulatory therapy
    - HBV viral prophylaxis (e.g., entecavir, tenofovir) recommended
    - Typically continued x 12 months post cessation of anti-CD20 Mab therapy
  - Other viruses (herpesvirus, PML)
  - PJP infection

Hwang JP et al. J Clin Oncol. 2020;38(31):3698.
Terrault NA et al. Hepatology. 2018;67(4):1560.

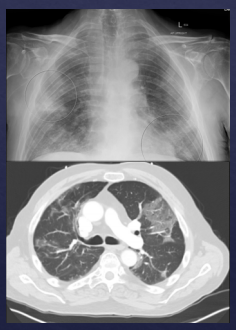
Biologic / Targeted Therapies
Monoclonal Antibodies

Case #2: 63 year old man with T-cell prolymphocytic leukemia on single-agent **alemtuzumab** therapy. Receiving acyclovir prophylaxis (for HSV/VZV) alongside pre-emptive screening with serial CMV PCR testing (all negative to-date).

Presents with a several week history of slowly progressing shortness of breath and new low-grade non-neutropenic fevers. CXR followed by cross-sectional chest imaging are shown (R).

This presentation is likely due to the **lack of** which of the following recommended prophylactic therapies?

A. Letermovir
B. Valganciclovir
C. Entecavir
D. Levofloxacin
E. Sulfamethoxazole-Trimethoprim ←



Biologic / Targeted Therapies
Monoclonal Antibodies

- Recognize **ALEMTUZUMAB**
  - Monoclonal Ab targeting CD52 (Anti-CD52 Mab) present on B and T lymphocytes, macrophages, and NK cells
  - Results in prolonged B- and T-cell depletion
- Infectious risks
  - Viral infections - especially herpesvirus (e.g. CMV, VZV, HSV)
  - Mycobacterial and fungal infections (e.g. PJP, *Aspergillus*)
- Infection prevention - viral and PJP prophylaxis typically given a minimum of 2 months after alemtuzumab and until CD4 ≥ 200 cells/mcL

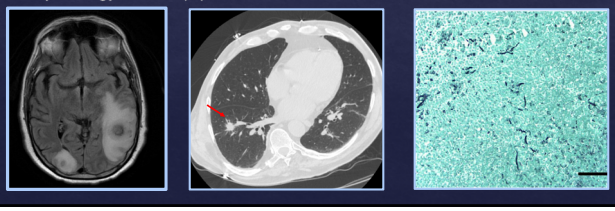
Biologic / Targeted Therapies
Bruton's Tyrosine Kinase (BTK) Inhibitors

Patient: 62 year old man, underlying CLL on **single-agent ibrutinib** x 4 months

Presentation: fevers, confusion, dysarthric with significant word finding difficulties

Imaging: brain MRI + chest CT

Histopathology: brain biopsy



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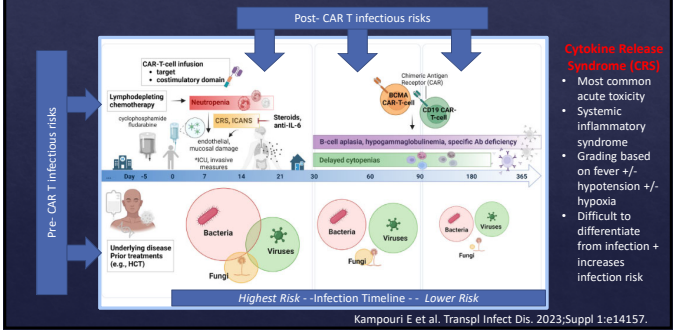
Biologic / Targeted Therapies

Bruton's Tyrosine Kinase (BTK) Inhibitors

- BTK inhibitors include - **Ibrutinib**, Acalabrutinib, Zanbrutinib
- Most commonly applied in CLL, lymphoma
- Block downstream activation of B-cell receptor pathway, cell growth, macrophage function
- Infectious risks include
  - Bacterial infections (most common)
  - Opportunistic fungal infections, inclusive of CNS involvement (e.g. *Aspergillus, Cryptococcus,* PJP)
- Infection prevention
  - Consider fungal (mold, PJP) and HSV/VZV prophylaxis if additional risk factors (inclusive of concomitant therapies)

Shah M et al. Transpl Infect Dis. 2024:e14283.

Chimeric Antigen Receptor T-cell Therapy



Cytokine Release Syndrome (CRS)

- Most common acute toxicity
- Systemic inflammatory syndrome
- Grading based on fever +/- hypotension +/- hypoxia
- Difficult to differentiate from infection + increases infection risk

Kampouri E et al. Transpl Infect Dis. 2023;Suppl 1:e14157.

Neutropenic Fever and "Syndromes"

Case #3

70 year old male with AML, recent initiation of azacitidine and venetoclax with neutropenic fever (102F) and fatigue

VS – 120/80, HR 100, RR 14, Sa02 96% on ambient air

Exam – no significant OP lesions, lungs cta, abd soft, nt/nd, no peri-rectal lesions/pain, no skin rash or lesions, no pain/redness/tenderness over central access site

Cultures – blood/urine pending

CXR – non-focal

Current Prophylaxis – levofloxacin and acyclovir

Prior infection history – none

Which of the following is the most appropriate change in therapy?

A. Levofloxacin → IV cefepime
B. Levofloxacin → IV cefepime + vancomycin
C. Levofloxacin → IV cefepime + metronidazole
D. Acyclovir → IV ganciclovir
E. Addition of antifungal therapy

Case #3 – Neutropenic Fever

- Empiric antibiotic therapy factors in prior therapies, infections/colonization, local epidemiology and clinical presentation
- Standard recommendations → monotherapy with an IV anti-pseudomonal β-lactam agent (e.g., cefepime, a carbapenem or piperacillin-tazobactam)
  - Caution with anti-pseudomonal beta-lactams lacking significant gram-positive coverage (e.g. ceftazidime)
- Addition/modification based on other factors
  - IV vancomycin → catheter-related infection, skins/soft tissue infection, pneumonia, hemodynamic instability
  - Alternate therapies → prior infection and/or colonization with MDR pathogens (e.g. methicillin-resistant *S. aureus*, vancomycin-resistance enterococcus, extended-spectrum and AmpC β-lactamase and/or carbapenemase-producing organisms)
  - Anaerobic coverage → select scenarios (e.g. intrabdominal infection such as neutropenic enterocolitis, peri-rectal abscess, necrotizing gingivitis/mucositis)

Freifeld AG et al. Clin Infect Dis. 2011;52(4):427.
Taplitz RA et al. J Clin Oncol. 2018;36(14):1443.

Case #4

PREVIEW QUESTION

35 year old woman with AML, day 15 of induction therapy.

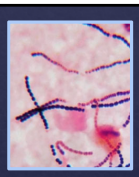
Presentation - fever, chills, diffuse erythematous rash.

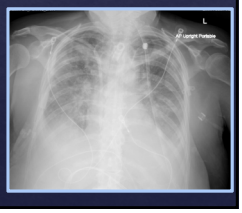
Exam – 100/62, HR 120, grade 2 oral mucositis, diffuse, blanching, erythematous rash.

Cultures - Blood cultures with **GPC in chains.**

CXR - bilateral diffuse infiltrates.

Prophylaxis - levofloxacin and acyclovir.





This is most consistent with infection with which of the following organisms?

A. *Streptococcus pneumoniae*
B. Coagulase-negative *Staphylococcus*
C. *Enterococcus faecalis*
D. *Streptococcus mitis*
E. *Stomatococcus mucilaginosus*

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Viridans Group Streptococci (VGS)

- VGS include *S. mitis, S. oralis*
- Normal flora of the oral cavity, upper respiratory and GI/GU tract
- Clinical presentation
  - Can include fevers, chills, flushing, stomatitis, pharyngitis
  - VGSS - toxic shock-like syndrome
    - Early vs late (2–3 days after presentation)
    - Hypotension, progression to respiratory failure and ARDS
    - Maculopapular rash starting on trunk and spreading centrifugally +/- desquamation of palms and soles
- Treatment: beta-lactams (increasing PCN resistance), vancomycin
- Case "clues": neutropenia, oral mucositis, high-dose cytarabine, fluoroquinolone prophylaxis

Shelburne et al. Clin Infect Dis. 2014;59(2):223.
Toonkel AR, Sepkowitz KA. Clin Infect Dis 2002;34(11):1524.

Testable Scenarios: Breakthrough BSIs

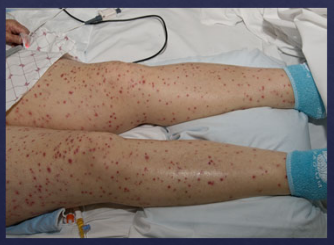
- Typical patient - neutropenic, progressive sepsis
- Recognize clinical presentation and holes in antimicrobial coverage
  - ARDS, rash, quinolones, mucositis → viridans Streptococci
  - Sepsis with β-lactams → *Stenotrophomonas,* Extended-spectrum (ESBL) and AmpC β-lactamase-Producing Enterobacterales
  - Sepsis with carbapenems → Carbapenem-resistant Enterobacterales/*Acinetobacter baumannii*
  - Lung and skin lesions → *P. aeruginosa*, fungi, *Nocardia*
  - Mucositis (upper, lower tract) → *Fusobacterium* spp., *Clostridium spp., Stomatococcus mucilaginosis*

Case #5

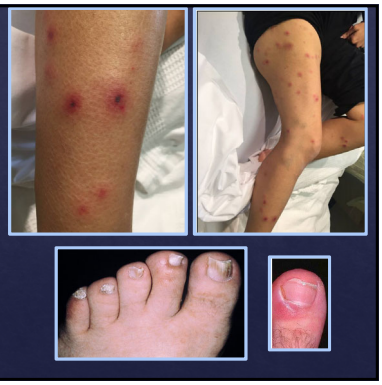
59 year old woman with AML with neutropenia for 25 days and now febrile for 6 days. She is receiving meropenem, vancomycin and acyclovir. Now with new skin lesions that are small, tender papules without central ulceration.

This is most consistent with infection with which of the following organisms?

A. *Rhizopus* spp.
B. Varicella zoster virus
C. *Cryptococcus neoformans*
D. Vancomycin resistant Enterococci
E. *Candida tropicalis*

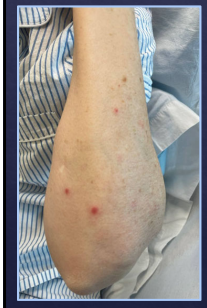


-35 year old woman with relapsed AML with dense neutropenia for over 30 days.
-Ongoing fevers with rapidly progressing, painful papular and nodular lesions, varying stages, some with central necrosis.
-Receiving meropenem, vancomycin, micafungin and acyclovir.
-Micro lab update that blood cultures are growing a "mold".

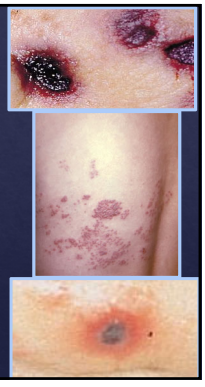


FUSARIOSIS

Skin Lesions



- Candidiasis
  - Small, tender papules
- Herpes
  - Vesicular
- *Aspergillus*
  - Ulcerative, necrotic
- Other filamentous fungi (*Fusarium* spp, *Scedosporium* spp)
- *P. aeruginosa*
  - Ecthyma gangrenosum

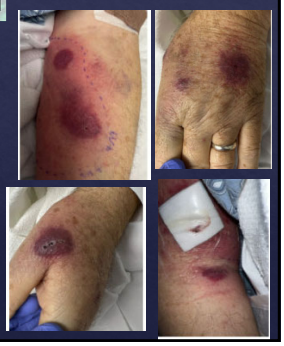


Case #6 PREVIEW QUESTION

70 year-old male with newly diagnosed AML developed erythematous, tender and edematous plaques over sites of trauma (blood draws, peripheral IV). He has been febrile to 38.7°C for the past several days.

The most likely etiology is:

A. *Candida albicans*
B. Sweet's syndrome
C. *Aspergillus niger*
D. Varicella Zoster virus
E. *Pseudomonas aeruginosa*



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Sweet's Syndrome

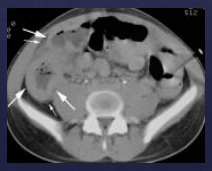
- Acute febrile neutrophilic dermatosis
- Variants: classic (idiopathic), malignancy-associated (hematologic, most common - AML), drug-induced
- Tender erythematous plaques and nodules (typical); also bullous, cellulitic, subcutaneous and necrotizing lesions
- Can demonstrate pathergy (lesions at site of trauma/injury)
- Classic stem: neutropenia resolving with GCSF assist, fever, skin lesions, cultures negative
- Treatment with steroids

Case #7

70 year old woman with AML receiving induction chemotherapy and neutropenic for 15 days. Develops fever, diarrhea and abdominal pain. Exam with decreased bowel sounds and tenderness with deep palpation in her RLQ. CT shows inflammation in cecum. Receiving levofloxacin and fluconazole prophylaxis. Four days prior to her admission for chemotherapy she ate out at a Chinese restaurant and had fried rice.

Which is the most likely etiology?

A. Norovirus
B. *Clostridioides (Clostridium) difficile*
C. Mixed anaerobic and aerobic bacteria
D. *Candida albicans*
E. *Bacillus cereus*



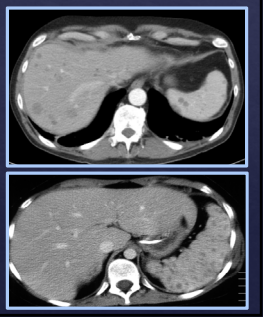
Neutropenic Enterocolitis

- AKA typhilitis, ileocecal syndrome
- Necrotizing inflammation with transmural infection of damaged bowel wall
- Related to cytotoxic chemotherapy, dense neutropenia
- Mixed infection with gram-negative, gram-positive, anaerobic bacteria and fungi
- Can be accompanied by bacteremia
  - Hint: mixed, anaerobic (*C. septicum, C. tertium, Bacteroides* spp.)
- Medical and (less often) surgical management

From: Xia R, Zhang X. World J Gastrointest Pathophysiol 2019;10(3):36.

Hepatosplenic Candidiasis

- Form of chronic disseminated candidiasis
- Clinical clues
  - Hematologic malignancy, preceding prolonged neutropenia, broad spectrum antibiotics
  - Fever, abdominal/flank pain, hepatosplenomegaly, nausea, vomiting
  - Occurring with neutrophil recovery/engraftment
  - Labs: abnormal hepatic panel (↑alk phos)
- *C. albicans* most common, blood cultures often negative
- Imaging: ultrasound, CT, MRI
- Differential: other fungi, bacteria, underlying malignancy
- Treatment: echinocandin or lipid formulation of amphotericin B, step-down course with oral azole (+/- steroids)



Pappas PG. Clin Infect Dis. 2016;62(4):e1.

Infections in Neutropenic Cancer Patients

Summary of Key Points

- Recognize typical infections associated with neutropenia and/or immunomodulatory therapies
- Predict breakthrough pathogens based on applied therapies
- Know specific syndromes
  - VGS sepsis
  - Differential of skin lesions
  - Invasive fungal infections in neutropenic patients
    - Sinopulmonary
    - Bloodstream
    - Hepatosplenic candidiasis
  - Neutropenic enterocolitis

Infections in Hematopoietic Cell Transplant Recipients

16 – Infections in the Neutropenic Cancer Patient and Hematopoietic Stem Cell Recipients

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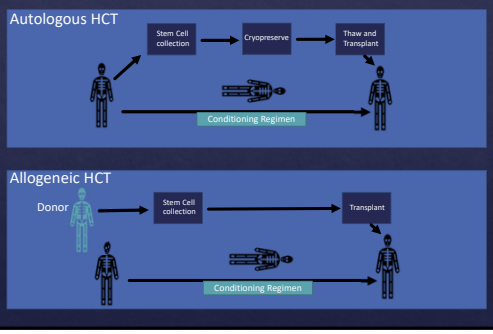
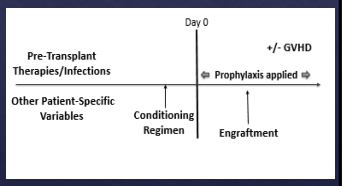
Fundamental Concepts



Fundamental Concepts

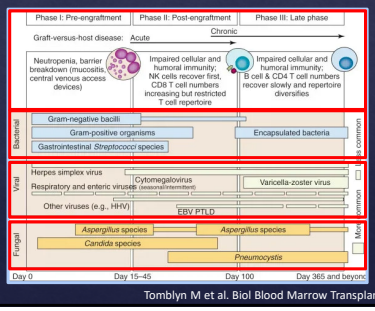
Transplant Variables and Infection Risk

- 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



Fundamental Concepts

Transplant Timeline



Tomblyn M et al. Biol Blood Marrow Transplant. 2009;15(10):1143.

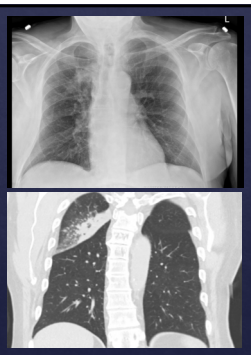
Case #1

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 posaconazole.



Case #1

What is the most likely cause of his current process?

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

Pulmonary Complications

Hematopoetic Cell Transplant

- Key elements of the question stem
  - Timing post transplant
  - Donor/recipient serologies
  - Applied prophylaxis
- Differential
  - **Infection**
  - Non-infectious "mimics"

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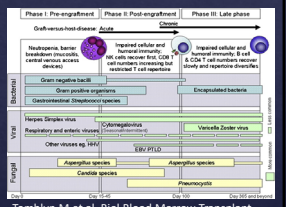
Pulmonary Complications

Infections

- Bacterial pathogens
  - *E. coli, P. aeruginosa, S. pneumonia, 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

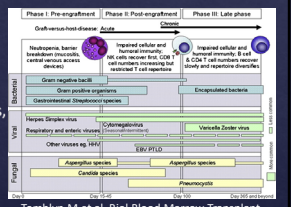


Tomblyn M et al. Biol Blood Marrow Transplant. 2009;15(10):1143.

Pulmonary Complications

Infection

- 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 delayed with primary prophylaxis
- Other (Toxoplasmosis, Strongyloidiasis)

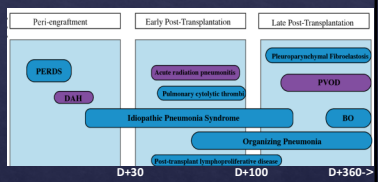


Tomblyn M et al. Biol Blood Marrow Transplant. 2009;15(10):1143.

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



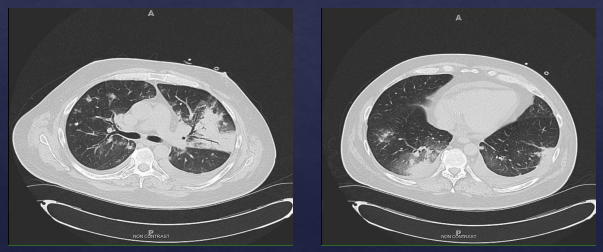
Adapted from: Astashchanka A et al. J Clin Med. 2021;10(15):3227.

Case #2

A 46 year old male **18 months s/p HLA mismatched HCT.** History of GVHD skin, GI tract, and lung. Treated with steroids 3 months ago. One month ago had Parainfluenza 3 with chest CT demonstrating tree-in-bud opacities in LLL. Received levofloxacin for 10 days.

He now has increasing shortness of breath and cough.

Case #2



Case #2

Blood cultures are negative. Sputum cultures grow oropharyngeal flora. Serum galactomannan is negative. What is the most likely cause of his current process?

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

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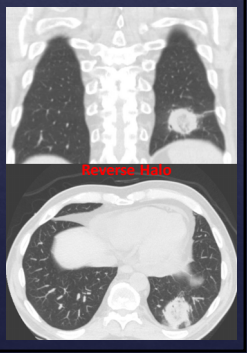
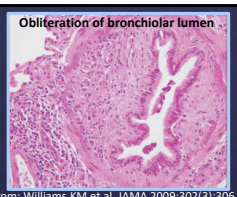
Pulmonary Complications
Late/Post Engraftment +

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

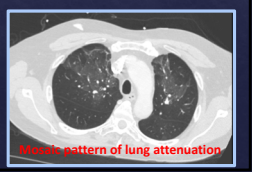


Pulmonary Complications
Bronchiolitis Obliterans

- Chronic GVHD of the lungs
- Chronic inflammatory and fibroproliferative process
  - Focused on terminal and respiratory bronchioles
  - Narrowing of the bronchiolar lumen → airflow obstruction (PFT detection)
- Clinical presentation with cough, increasing shortness of breath and dyspnea on exertion

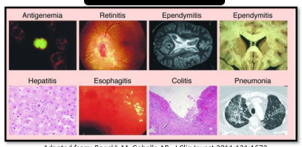


From: Williams KM et al. JAMA 2009;302(3):306.



CMV Infection in HCT
The "Troll of Transplant"

Direct Effects



Adapted from: Boeckh M, Geballe AP. J Clin Invest 2011;121:1673.

Indirect Effects

- Bacteremia
- Invasive Fungal Infections
- GVHD
- Non-Relapse Mortality

CMV Risks

- CMV Seropositivity (R+ >>> D+/R- >> D-/R-)
- GVHD and associated therapies (e.g. steroids, particularly prednisone > 1mg/kg/day)
- T-cell depletion (e.g. alemtuzumab, ATG)
- Cord blood transplant
- Haploidentical, mismatched/unrelated donors
- Older Age
- Lymphopenia

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

CMV Infection in HCT
Prevention

Pre-Emptive

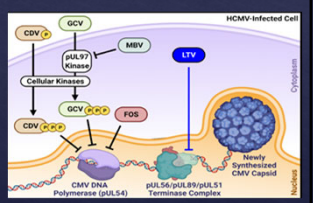
- Weekly CMV DNA PCR monitoring through at least day +100
- CMV DNAemia > threshold = initiation of antiviral
  - Typical therapy – (val)ganciclovir >> foscarnet

Primary Prophylaxis

- Initiated by day +28 through at least day +100 in highest risk (R+)
- Letermovir (FDA-approved)
  - Lacks side effects - cytopenias and nephrotoxicity
  - Lacks activity against HSV/VZV
  - Relevant DDI (azoles, calcineurin inhibitors)

CMV Infection in HCT
Treatment of Infection/Disease

- Induction therapy and maintenance 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 now approved
    - 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.

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

16 – Infections in the Neutropenic Cancer Patient and Hematopoietic Stem Cell Recipients

Speaker: Jennifer Saullo, MD

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.

Case #3

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.

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

A. Perform serum VZV PCR
B. Empiric corticosteroid treatment
C. Send *Clostridioides difficile* stool testing and start oral vancomycin
D. CMV PCR, stool *C. difficile*, bacterial culture
E. Choice D *and* upper, lower endoscopy

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

GVHD in HCT

GI manifestations (infection mimic)

Hepatitis	Diarrhea
GVHD	GVHD
Herpesviruses (CMV, VZV, HSV)	CMV
Other viral hepatitis	*C. difficile*
Hepatitis B (less common A/C/E)	Norovirus (chronic diarrhea)
Adenovirus	Adenovirus

Case #4

40 year old male, d+60 following allogeneic HCT from a MUD presents with bloody urine for 6 days. Has skin GVHD and initiated on high-dose prednisone (1mg/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.

The most likely etiology is:

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

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)

16 – Infections in the Neutropenic Cancer Patient and Hematopoietic Stem Cell Recipients

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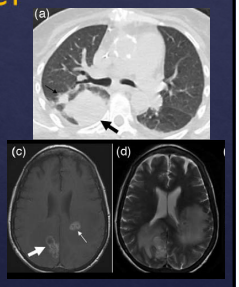
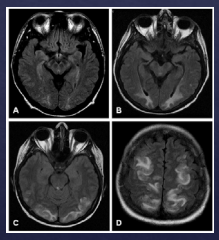
Neurologic Syndromes in HCT

- Infection
  - Viral pathogens
    - Herpes viruses – HSV, VZV, CMV, **HHV-6***, EBV
    - West Nile virus
    - JCV – PML
  - Pulmonary – CNS lesions
    - Invasive fungal infections
    - *Nocardia*
    - Toxoplasmosis
- Non-Infectious
  - Antibiotics – carbapenems, cefepime
  - Posterior reversible encephalopathy syndrome (PRES)



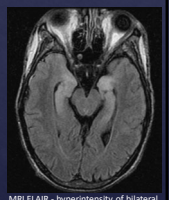
Neurologic Syndromes in HCT

- Infection
  - Viral pathogens
    - Herpes viruses: HSV, CMV, **HHV-6***
    - West Nile virus
    - JCV – PML
  - Pulmonary – CNS lesions
    - Invasive fungal infections
    - *Nocardia*
    - Toxoplasmosis
- Antibiotics - carbapenems, cefepime
- Posterior reversible encephalopathy syndrome (PRES*) – calcineurin inhibitors



Human Herpes Virus-6 (HHV-6) in HCT

- HHV-6 seroprevalence > 95% after age 2
  - Viremia common post-allogeneic HCT (~ 40-60%)
  - Clinical associations - rash, fever, myelosuppression, hepatitis, pneumonitis
- **Meningoencephalitis**** (testable manifestation; HHV-6B)
  - Nonspecific presentation (confusion, memory loss, seizures; EEG / MRI: temporal region)
  - Generally early post-transplant (~ D+60)
  - Risks include mismatched/unrelated donors, umbilical cord blood; T-cell depletion
- Diagnosis: PCR of CSF
- Chromosomal integration
- Treatment: ganciclovir, foscarnet >> cidofovir (acyclovir resistant)



MRI FLAIR - hyperintensity of bilateral mesial temporal areas including uncl/hippocampi; From: Yassin A et al. Ann Med Surg. 2020;60:81.

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

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

Thank You

Questions/Comments:

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