Infections in the Neutropenic Cancer Patient and Hematopoietic Stem Cell Recipients

Goals of This Review

- Focus on testable complications specific to the immunocompromised host
  - Types of immune-suppressing drugs and diseases
  - Recognition of specific “neutropenic syndromes”
    - Skin lesions
    - Invasive fungal infections
    - Neutropenic colitis

Fundamentals: Underlying disease risks

- Immune defects associated with underlying malignancy (and prior therapies)
  - AML and myelodysplastic syndromes (MDS)
    - Qualitative and quantitative neutropenia
  - Lymphoma
    - Functional asplenia
  - CLL and multiple myeloma
    - Hypogammaglobulinemia
  - Aplastic anemia
    - Severe, prolonged neutropenia

Fundamentals: Therapeutic risks

- Recognize risks with cytotoxic therapy (neutropenia)
  - Prolonged (>10 days) and profound (< 500 cells / mm3) leads to high risks for severe bacterial and fungal infections
    - Bacteremia, pneumonia, candidemia, aspergillosis
    - Outcomes tend to be poor – preventative therapies important
- Recognize infectious risks with other biologic therapies that immunosuppress
  - T cell suppressing agents and ‘targeted’ biologics
    - Viral and fungal infections

Imune modulating anti-cancer drugs

- Drugs that impact neutrophils
  - Many cytotoxic agents
    - Bacterial infections, fungal infections
- Drugs that impact T cells
  - Purine analogs (fludarabine, cladribine, clofarabine) and temozolomide
    - CD4+ T cell dysfunction: Herpes viruses (CMV, VZV), intracellular bacteria, fungi (PJP, Aspergillus)

Disclosures of Financial Relationships with Relevant Commercial Interests

- Consultant: Cidara, Merck and Company, Sfunga Therapeutics
- Ownership Interests: MycoMed Technologies
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Speaker: Kieren Marr, MD

**Bendamustine**
- Nitrogen-based alkylating and antimetabolite
- Indolent non-Hodgkin lymphomas, CLL
- Neutropenia and lymphopenia (months - years)
- Higher risks for infections (bacterial, CMV, PJP, histoplasmosis)


**Biological Therapies**
- Generally broken into three categories
  - Biological response modifiers. Exert effects by stimulating immune system (ex. CSFs)
  - Gene therapies
  - Targeted therapies (mAbs and small molecule enzyme inhibitors)

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Series of articles by European Study Group for Infections in Compromised Hosts

*Supplement in Clin Microbiol and Infect 24, 2018*

**Key anti-CD Monoclonal Abs**
- Common antibodies that impact B and T cells
  - Rituximab (anti-CD20)
  - B cells: CLL, lymphoma
  - Loss of vaccine responses, responses to encapsulated bacteria (pneumonia), Herpes B reactivation, PMK
  - Alemtuzimab (anti-CD52)
  - T and B cell depletion for a long time (about 6 months): lymphoma, leukemia, BMT (graft vs. host disease treatment)
  - Herpes viruses (esp. CMV), fungal infections (PJP, Aspergillus)

**Tyrosine kinase inhibitors**
- BCR – ABL Tyrosine – kinase inhibitors
  - Inhibit signal transduction through BCR-ABL oncogene (ex. imatinib, dasatinib, nilotinib)
  - CML. Think T and B cells (VZV, Hep B reactivation)
  - Autoimmune pneumonitis and colitis (infection mimic)
  - Aspergillosis and other IFI

**Bruton’s tyrosine kinase inhibitors**
- Ibrutinib
- B cell development, macrophage phagocytosis
- Lymphoid malignancies (ex. CLL, lymphomas)
- Single-center review: 11%
- Fungal, bacterial infections – Aspergillosis (including CNS)
- Autoimmune – idiopathic drug “toxicities”: colitis, pneumonitis

*Varughese et al. Clin Infect Dis 2018; 67(5): 687-92*
*Bercusson A. Blood 2018 132(18): 1985-88*
*Blez et al. Haematologica 2019 (in press)*
Checkpoin inhibitors

- Block immune checkpoints that regulate T cell activation / function – multiple tumors
- Targeting PD-1 on T cells (pembrolizumab, nivolumab, cemiplimab) or PD-L1 on tumor cells (atezolizumab, avelumab, durvalumab)
- Targeting CTLA-4 on T cells (ipilimumab)
- Induce colitis, pneumonitis
- Increased risks for infection in people receiving concurrent steroids, TNF-α targeting agents for above

Venetoclax

- Inhibits anti-apoptotic BCL2 – family proteins (AML, lymphoid malignancies)
- Sometimes given with hypomethylating agents for AML (ex. azacytidine)
  - Severe, prolonged neutropenia – bacterial, fungal infections
  - Drug interactions may limit use of azole prophylaxis
    - Cyp3a inhibition requires VEN dose decrease / toxicities
- Aspergillosis increasingly recognized

Neutropenic “syndromes”

- Key points: neutropenia, mucositis, high-dose cytosine arabinoside, fluoroquinolone
- Can present with fever, flushing, chills, stomatitis, pharyngitis
- VGS shock syndrome:
  - After 24-48 hours, hypotension in 1/3 of cases
  - Rash, shock, ARDS in 1/4 of cases (similar to toxic shock)
- Endocarditis unusual (<10%)
- S. mitis, S. oralis
- Vancomycin
- Mortality high (15-20%)

Viridans Streptococci

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Testable contexts:
Breakthrough Bloodstream Infections

- Typical patient- neutropenic, progressive sepsis
- Recognize holes in protection, specific syndromes
  - ARDS, rash, quinolones, mucositis → viridans Streptococci
  - Sepsis with β-lactams → Stenotrophomonas, ESBL
  - Sepsis with carbapenems → KPC
  - Lung and skin lesions → P. aeruginosa, Fungi
  - Skin lesions, gram + → Corynebacterium jeikeium
  - Mucositis (upper, lower tract) → Fusobacterium spp., Clostridium spp., Stomatococcus mucilaginosus

35 year old woman with AML day 15 after induction therapy.
Fever, chills, diffuse erythematous rash. Blood culture + GPC in chains
Exam – 100/62, HR 120, grade 2 oral mucositis, and a diffuse, blanching, erythematous rash. CXR - bilateral diffuse infiltrates. She is receiving 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
Question #2

59 year old woman with AML with neutropenia for 25 days. She has been febrile for 6 days, and is receiving meropenem, vancomycin, and acyclovir. New skin lesions that are small, papular, and tender with no central ulceration.

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

Skin Lesions

- Candidiasis
  - Small, tender papules
- Herpes
  - Vesicular
- Aspergillus
  - Ulcerative, necrotic
- Other filamentous fungi (Fusarium, P. boydii)
  - Multiple, erythematous, different stages
- P. aeruginosa
  - Ecthyma gangrenosum

Fusarium

- Invasive pulmonary disease with skin lesions
- Locally invasive infections in neutropenic patients
  - Keratitis
  - Onychomycosis

Sweet’s syndrome

- Acute febrile neutrophilic dermatosis
- Variants: classic (idiopathic), malignancy-associated, drug induced
- Tender erythematous plaques and nodules typical; also bullous, cellulitic, necrotizing lesions
- Classic stem: neutropenia resolving with GCSF assist, fever, skin lesions, cultures - negative
- Steroids

Question #3

50 year old woman with newly diagnosed AML developed tender, pruritic plaques and plaques on her neck. She had been febrile 38.7°C for the past several days and had received a dose of G-CSF 3 days earlier, with rapid WBC increase (900 ANC). Most likely etiology:

A. Candida albicans
B. Sweet’s syndrome
C. Aspergillus niger
D. Varicella Zoster Virus
E. Pseudomonas aeruginosa


Sweet’s syndrome

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Question #4

70 yr old woman with AML, neutropenia for 55 days, s/p induction chemotherapy develops fever, diarrhea, and abdominal pain. Exam - decreased bowel sounds and tenderness with deep palpation in her RLQ. CT shows inflammation in cecum. Levofloxacin and fluconazole prophylaxis. 4 days prior to her admission for chemotherapy, she ate Chinese food with 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

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Neutropenic Enterocolitis

- Neutropenic enterocolitis (typhlitis)
  - Necrotizing inflammation with transmural infection of damaged bowel wall
  - Mixed infection with gram-negative, gram-positive, anaerobic bacteria, fungi
  - Can be accompanied by bacteremia
    - Hint: mixed, anaerobic
      (C. septicum, C. tertium, B. cereus)
  - Medical and (less often) surgical management

Hepatosplenic Candidiasis

- Inflammatory response to fungi invaded by portal vasculature
- Presentation after engraftment: abdominal pain, increased LFTs (alk phosph), fever, leg / flank pain
- Differential: other fungi, bacteria, lymphoma
- C. albicans most common
  - Amphotericin B primary therapy followed by prolonged fluconazole, echinocandins

Summary: PEARLS

- Recognize typical infections associated with neutropenia and/or other immune suppression (biologic inhibitors of cellular defenses)
- Predict breakthrough bloodstream pathogens based on therapy
- Know specific syndromes
  - S. viridans sepsis – ARDS
  - Differential of skin lesions
  - Neutropenic patients - IFI
    - Pulmonary
    - Bloodstream
    - Hepatosplenic candidiasis
  - GI tract enterocolitis

Thank you

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