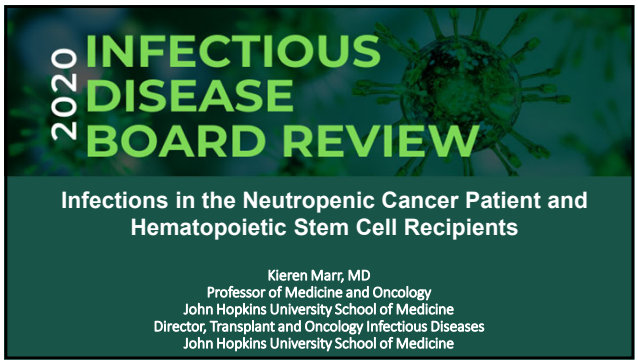
41a – Infections in the Neutropenic Cancer Patient and Hematopoietic Stem Cell Recipients

Speaker: Kieren Marr, MD



Disclosures of Financial Relationships with Relevant Commercial Interests

- Consultant – Amplyx, Cidara, Merck and Company, Sfunga Therapeutics
- Ownership Interests – MycoMed Technologies

Goals of This Review

- Immune compromised people develop "typical" infections and those specific to their underlying risks
- Focus here on testable complications specific to the host
  - Types of immune – suppressing drugs and diseases
  - Recognition of specific "neutropenic syndromes"
    - Skin lesions
    - Invasive fungal infections
    - Neutropenic colitis

Testable Concepts

- Think about the patient
  - How does underlying disease impact risks?
- Think about the treatment received
  - What type of immune suppression?
- Think about infections breaking through preventative therapies
  - A good context to test resistance and differentials
- Think about common non-infectious syndromes

Fundamentals: Host Immune Risks

- Neutropenia
  - Prolonged (>10 days) and profound (< 500 cells / mm3) associated with high risks for severe bacterial and fungal infections
    - Bacteremia, pneumonia, candidemia, aspergillosis
- Infectious risks associated with biologics – or medical immune suppression

Classic Immunologic 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

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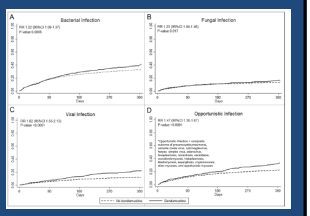
Immune modulating anti-cancer drugs

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

Bendamustine

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



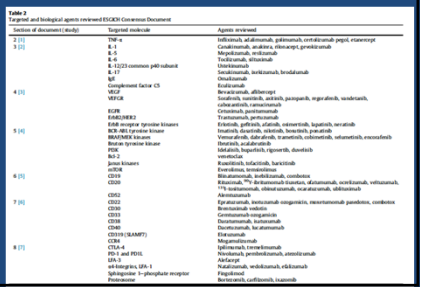
Fung et al. Clin Infect Dis 68(2): 247-55

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)

For a more robust review

- 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). Hepatitis B reactivation, PML
  - 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)
    - Aspergillosis and other IFI
    - Autoimmune pneumonitis and colitis (infection mimic)

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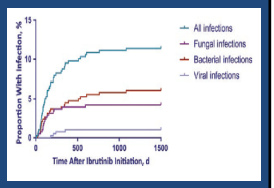
Bruton's tyrosine kinase inhibitors

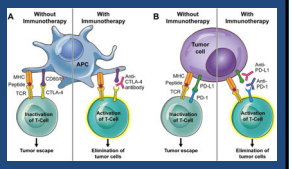
- Ibrutinib
- B cell development, macrophage phagocytosis
- Lymphoid malignancies (ex. CLL, lymphomas)
- Single-center review: 11%
- Fungal, bacterial infections
  - Aspergillosis (including CNS)
- Autoimmune – idiopathic drug "toxicities": colitis, pneumonitis



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)

Checkpoint 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 (ipilumumab)
- Induce colitis, pneumonitis
- Increased risks for infection in people receiving concurrent steroids, TNF-α targeting agents for above



Soularue et al. BMJ gut 2018

Neutropenic "syndromes"

Notes about fever during neutropenia

- Develop a differential based on preventative drugs already in use and other syndromes (pneumonia, colitis)
- Broad coverage, examination, cultures
- Inpatient – outpatient management guidelines, but not testable in this setting
- Duration of therapy is controversial
  - Cochran Database review 2019: could not make any strong conclusions regarding efficacy, safety of short vs. long course antibiotic therapy

Stern et al. CDSR 2019

Question #1

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*

Viridans Streptococci

- 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%)

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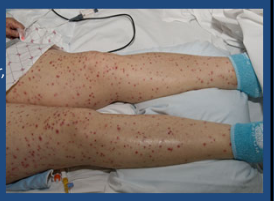
Testable contexts: Breakthrough Bloodstream Infections

- 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 carbepenems → KPC
  - Lung and skin lesions → *P. aeruginosa*, Fungi
  - Skin lesions, gram + → *Corynebacterium jeikeium*
  - Mucositis (upper, lower tract) → *Fusobacterium* spp., *Clostridium spp., Stomatococcus mucilaginosis*

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*

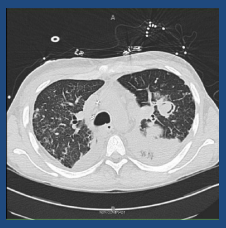
Fungal Infections

- Candida infections
  - Frequent in patients not receiving prophylactic antifungals
    - *C. albicans, C. tropicalis*
    - Mucositis, colonization, neutropenia
    - Acquired through GI tract or catheter
    - Organisms in patients receiving azole prophylaxis
      - *C. glabrata, C. krusei*
      - *C. parapsilosis*
        - » catheter / intravenous infusates
- Mold infections
  - *Aspergillus fumigatus* most common
  - Risk increases with duration of neutropenia or prior neutropenic episodes

Question #3

INFECTIOUS DISEASE BOARD REVIEW PREVIEW QUESTION

43 yr old F with AML with fever, cough and nodular lung lesions 20 days after induction therapy. On meropenem, fluconazole, acyclovir. Voriconazole begun for presumed aspergillosis. CT scan 10 days later showed lesion doubled in size with slight cavitation. ANC has risen from 25 to 800. Clinically she is improving.

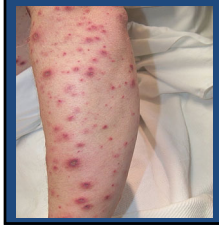


A. Change voriconazole to liposomal amphotericin B
B. Change voriconazole to posaconazole
C. Continue to follow on current therapy
D. Add micafungin
E. Bronchoscopy for diagnosis

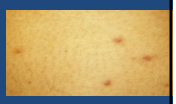
Pulmonary fungal infections

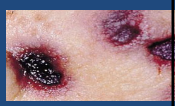
- *Aspergillus* species most common
- Nodular, tracheobronchial abnormalities (sometimes with 'halo') that enlarge before necrotizing
- Alternative microbial diagnosis
  - Fusarium, Scedosporium, others
  - Mucormycoses

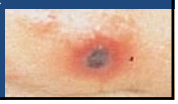
Skin Lesions



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







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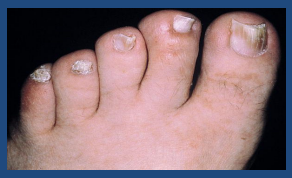
Fusarium

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

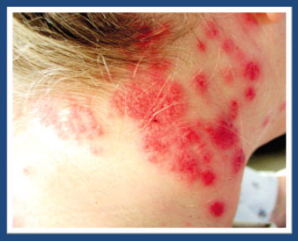


Question #4

2020 INFECTIOUS DISEASE BOARD REVIEW PREVIEW QUESTION

50-year-old woman with newly diagnosed AML developed tender, pruritic papules 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*



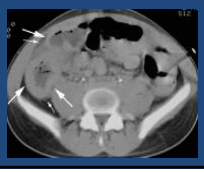
Haverstock, C. et al. Arch Dermatol 2006;142:235-b-240-b.

Question #5

70 yr old woman with AML, neutropenic for 15 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.

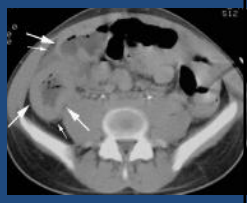
Which is the most likely etiology?

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



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

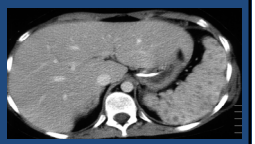


GI Infections

- Diarrhea is a common complaint
  - Mucositis from cytotoxic therapy
  - Tips for infections
    - Bloody, fever, abdominal pain
- Colitis / enteritis
  - Neutropenic enterocolitis
  - *C. difficile* colitis

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



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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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