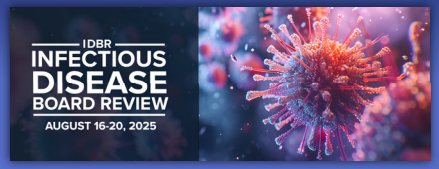

Infections in Neutropenic Cancer Patients

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8/4/2025

1

Disclosures of Financial Relationships with Relevant Commercial Interests

- Chapter author – UpToDate

2

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”

3

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*

4

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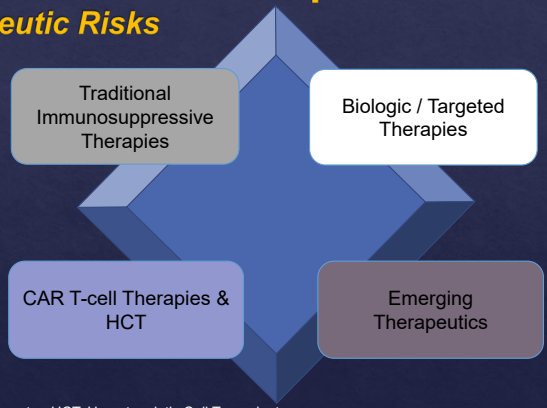
Fundamental Concepts
Therapeutic Risks



CAR: Chimeric Antigen Receptor; HCT: Hematopoietic Cell Transplant

5

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

6

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

7

Biologic / Targeted Therapies
Monoclonal Antibodies

8

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Question #1

A 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

9

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 at least 12 months post cessation of anti-CD20 Mab therapy
  - Other viruses (herpesvirus, PML)
  - Pneumocystis jirovecii infection

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

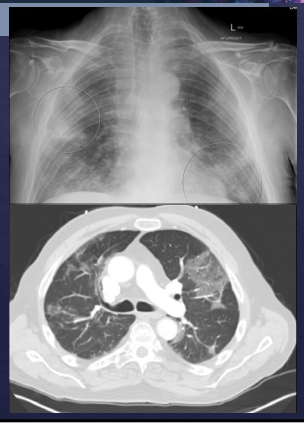
10

Question #2

PREVIEW QUESTION

63-year-old man with T-cell prolymphocytic leukemia on single-agent **alemtuzumab** therapy. Receiving acyclovir prophylaxis (for HSV/VZV) alongside preemptive therapy for CMV (serial CMV PCR testing negative to-date).

Presents with 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).



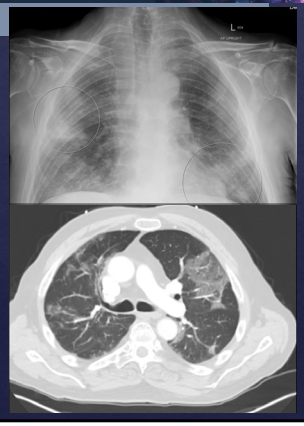
11

Question #2

PREVIEW QUESTION

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



12

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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

13

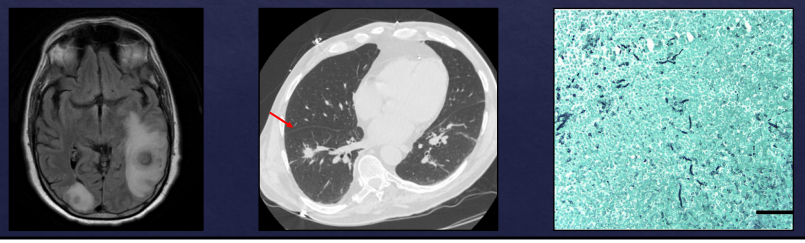
Biologic / Targeted Therapies
Bruton's Tyrosine Kinase (BTK) Inhibitors

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



14

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.

15

Question #3

61-year-old patient with relapsed/refractory diffuse large B-cell lymphoma (DLBCL) with extensive prior DLBCL-directed therapies. Received lymphodepleting chemotherapy with fludarabine and cyclophosphamide and is now day +2 following CD-19 directed CAR T-cell therapy with Axicabtagene ciloleucel (Yescarta®). Prophylaxis includes valacyclovir, levofloxacin, fluconazole and SMX-TMP.

Develops neutropenic fever to 102, hypotension requiring low dose norepinephrine (BP 90/60, despite IVF resuscitation), tachycardia (HR 120s) and hypoxia (SaO2 90%). Blood cultures, urinalysis and urine culture are submitted and CXR and CT chest show mild bilateral ground glass opacities and small pleural effusions. Labs notable for WBC 0.5, stable Hgb, platelets and comprehensive metabolic panel, CRP 4.0->10mg/dL, ferritin 200->2000 ng/mL.

16

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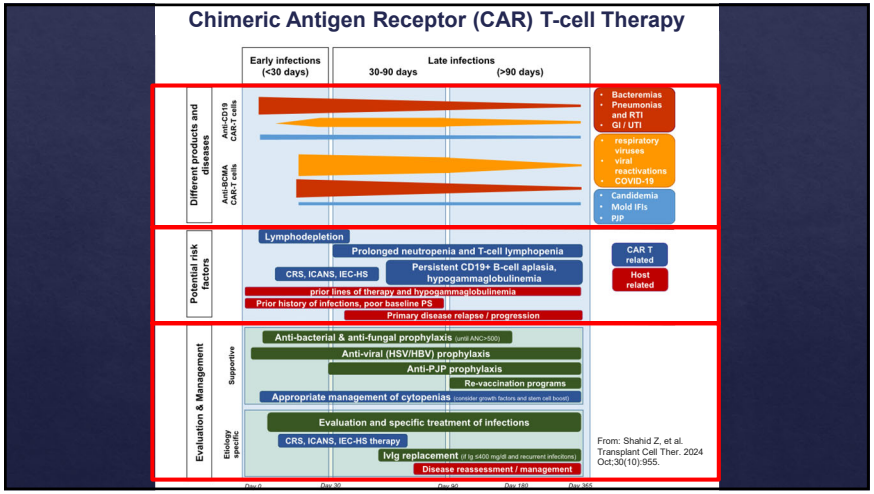
Question #3

Which of the following is the most appropriate management?

A. Modify antimicrobials: levofloxacin → IV cefepime + vancomycin and administer tocilizumab
B. Modify antimicrobials: fluconazole → IV liposomal amphotericin B
C. Modify antimicrobials: valacyclovir→ IV ganciclovir
D. Administer tocilizumab x 1 dose

17



18

Chimeric Antigen Receptor (CAR) T-cell Therapy

- **Cytokine release syndrome** - supraphysiologic response following any immune therapy with activation or engagement of endogenous or infused T cells and/or other immune effector cells
  - Timeline – typically within first 2 weeks of CAR T-cell infusion, median onset 2-3 days
  - Symptoms – must include fever, and may include hypotension, capillary leak (hypoxia) and end organ dysfunction
  - Management – supportive care (including ID-related investigation and empiric antimicrobials + CRS directed therapies (tocilizumab +/- glucocorticoid)
- **Immune effector cell-associated neurotoxicity syndrome (ICANS)** - pathologic process involving the central nervous system following any immune therapy that results in the activation or engagement of endogenous or infused T cells and/or other immune effector cells
  - Timeline – biphasic (early, often overlaps with CRS vs late, 2-4 weeks after CAR T-cell infusion)
  - Symptoms – may include aphasia, altered level of consciousness, impairment of cognitive skills, motor weakness, seizures, and cerebral edema
  - Management includes – supportive care + glucocorticoids + antiseizure therapies

Lee DW et al, Biol Blood Marrow Transplant. 2019;25(4):625.

19

Neutropenic Fever and "Syndromes"

20

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Question #4

PREVIEW QUESTION

- 70-year-old male with AML and recent initiation of azacitidine and venetoclax presenting 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

21

Question #4

PREVIEW QUESTION

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

22

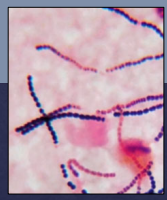
Question #4 – Neutropenic Fever

- Empiric antibiotic therapy factors in prior therapies, infections/colonization, local epidemiology and clinical presentation
- Standard recommendations→ monotherapy with anti-pseudomonal β-lactam agent (e.g., cefepime, a carbapenem or piperacillin-tazobactam)
  - Caution with anti-pseudomonal β-lactams lacking significant gram-positive coverage (e.g., ceftazidime)
- Addition/modification based on other factors
  - IV vancomycin → catheter-related infection, skin/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)

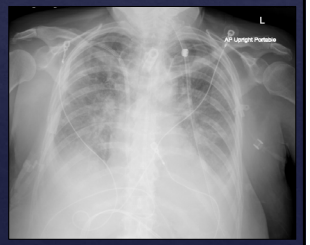
Freifeld AG et al. Clin Infect Dis. 2011;52(4):427.
Taplitz RA et al. J Clin Oncol. 2018;36(14):1443.

23

Question #5



- 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



24

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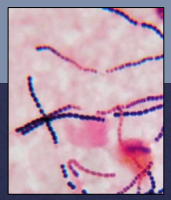
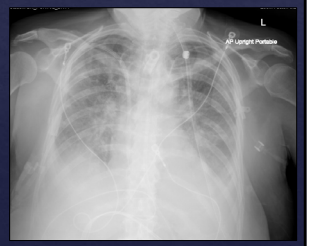
Question #5



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*

25

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.

26

Testable Scenarios: Breakthrough BSIs

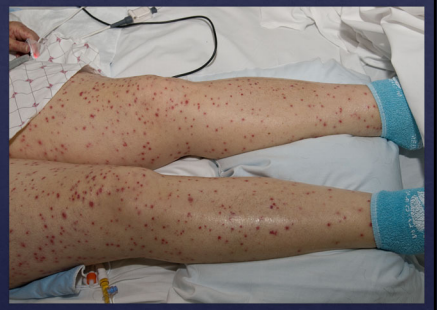
- Typical patient - neutropenic, progressive sepsis
- Recognize clinical presentation and holes in antimicrobial coverage
  - **ARDS, rash, quinolones, mucositis** → viridans Streptococci
  - **Sepsis with β-lactams** → *Stenotrophomonas* (exceptions), Extended-spectrum (ESBL) and AmpC β-lactamase-Producing 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*

27

Question #6

PREVIEW QUESTION

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



28

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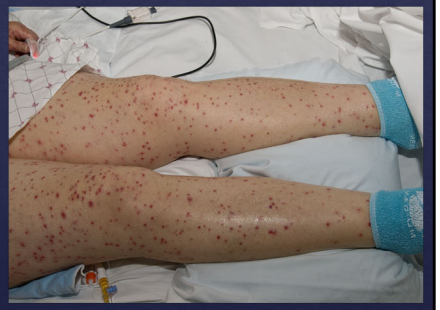
Question #6

PREVIEW QUESTION

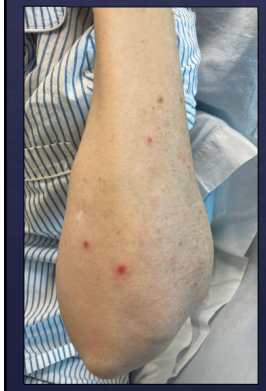
This is most consistent with infection with which of the following organisms?

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

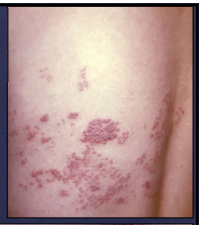


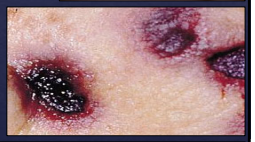
29

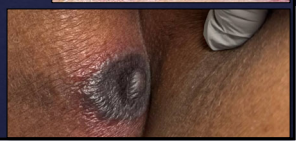
Skin Lesions



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



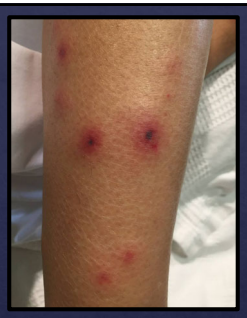


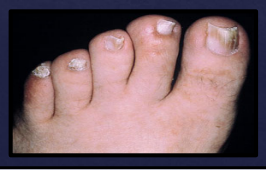


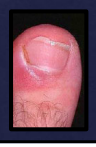
30

Fusariosis

- 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"



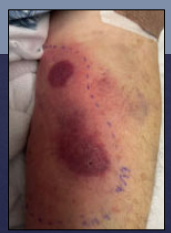


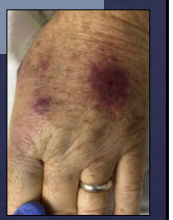


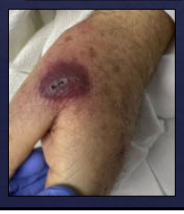
31

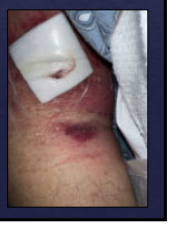
Question #7

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.









32

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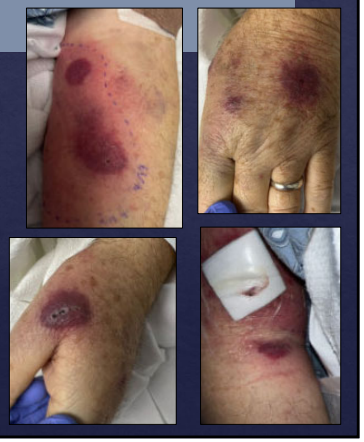
Question #7

What is the most likely etiology?

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



33

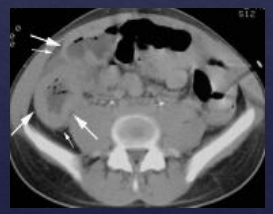
Sweet's Syndrome

- 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

34

Question #8

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.

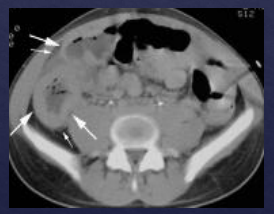


35

Question #8

Which is the most likely etiology?

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



36

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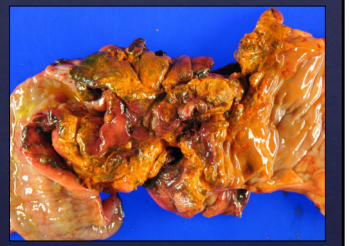
Neutropenic Enterocolitis

- 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

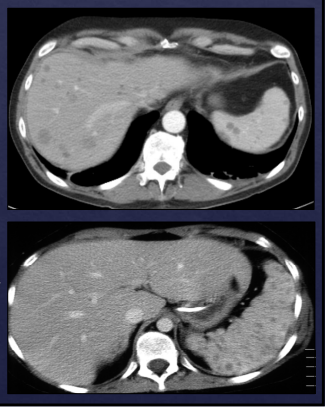


From: Xia R, Zhang X. World J Gastrointest Pathophysiol 2019;10(3):36.

37

Hepatosplenic Candidiasis

- Form of chronic disseminated candidiasis
- Clinical clues
  - Hematologic malignancy, 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.

38

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

39

Thank You

Questions/Comments:

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40

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