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Multidisciplinary Approaches to Cancer Symposium

Frequent Infectious Disease Complications from Treatments of Hematologic Malignancies

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City of Hope

Disclosures

- Grant/Research Support from AlloVir, Ansun Biopharma, Gilead, Karius, and Merck.
- Consultant for AlloVir, Merck, and Takeda.
- On the Speakers Bureau for Merck and Takeda.
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This presentation and/or comments will provide a balanced, non-promotional, and evidence-based approach to all diagnostic, therapeutic and/or research related content.

This presentation has been peer-reviewed and no conflicts were noted.

The off-label/investigational use of Fosmanogepix, and Olorofim will be addressed.

Cultural Linguistic Competency (CLC) & Implicit Bias (IB)

STATE LAW:

The California legislature has passed Assembly Bill (AB) 1195, which states that as of July 1, 2006, all Category 1 CME activities that relate to patient care must include a cultural diversity/linguistics component. It has also passed AB 241, which states that as of January 1, 2022, all continuing education courses for a physician and surgeon **must** contain curriculum that includes specified instruction in the understanding of implicit bias in medical treatment.

The cultural and linguistic competency (CLC) and implicit bias (IB) definitions reiterate how patients' diverse backgrounds may impact their access to care.

EXEMPTION:

Business and Professions Code 2190.1 exempts activities which are dedicated solely to research or other issues that do not contain a direct patient care component.

The following CLC & IB components will be addressed in this presentation:

- *Infections in elderly may present atypically compared to younger adults, leading to delay in diagnosis.*
- *The need to understand that presence or absence of fever should not allow bias in evaluating for infection in elderly patients.*

Hematologic malignancies

- Myeloid: AML/ MDS, ALL
  - Neutropenia, mucositis, typhlitis/ enterocolitis
  - Prolonged prophylactic antibacterials/ antifungals – breakthrough infections with resistant pathogens
- Lymphoid: Lymphoma's, CLL
  - B cell and T cell immunodeficiency depending on therapeutic intervention
- Plasma cell: multiple myeloma
  - Increased risk for infections with encapsulated bacteria
  - Depends on therapeutic interventions, such as bispecifics.

Common syndromes

- Neutropenic fever – recommend IDSA/ NCCN guidelines
- Pneumonia/ Invasive mold infections – will discuss illustrative case
- Central Venous Catheter related infections – IDSA guidelines
- Gastrointestinal infections
- Dermatologic
- Hepatitis B and C prevention and treatment – ASCO guidelines

Neutropenic Fever

- Definition: single oral temperature of > 38.3C or a temperature >38C sustained over 1 hour
- Neutropenia; ANC of <500/ mm3 or one that is expected to fall below 500/mm3 over next 48 hours
- Profound neutropenia < 100 cells/mm3
- Functional neutropenia – hematologic malignancy resulting in qualitative defects

Neutropenic Fever

- Risk stratification (low vs. high) - starting point for management

- Assessment of risk for complications of severe infection at presentation with fever – helps determining:
  - type of empirical antibiotics (oral vs. iv),
  - setting (OP vs. IP) and
  - duration of antibiotics

Neutropenic Fever
Risk Assessment

- High risk:
  - prolonged neutropenia (>7days),
  - profound neutropenia (<100/ mm3 following cytotoxic chemotherapy),
  - and or significant co-morbid conditions, including hypotension, pneumonia, new onset abdominal pain or neurologic changes.

- High risk patients should be hospitalized for management

Neutropenic Fever
Risk Assessment

- Low Risk
  - ANC > 100 cells/mm3
  - neutropenia anticipated to last < 7 days
  - No IV catheter site infection
  - No appearance of illness (no localizing s/s)
  - No co-morbid conditions or complications (shock, hypoxia, pneumonia or other deep-organ dysfunction, vomiting or diarrhea)

- Low risk patients are candidates for oral therapy

Neutropenic Fever
Clinical presentation

- Most remarkable is lack of physical findings in febrile neutropenic patients
- Above is due to absence of inflammatory response at infection site.
- Even patients with pneumonia may lack symptoms
- Perirectal abscess maybe relatively asymptomatic

Neutropenic fever
Empiric antibiotic Therapy

- High risk – admit and give iv antibiotics

- Monotherapy with an anti-pseudomonal b-lactam agent (cefepime, ceftazidime, carbapenem, or piperacillin/ tazobactam)
- Other agents such as quinolones, aminoglycoside maybe added for management of complications (eg., hypotension, pneumonia)
- Vancomycin is not suggested as initial agent unless specific clinical indication exists – such as CVC infection, skin/ soft tissue infection, pneumonia or hemodynamic instability

- Afebrile neutropenic patient with new signs or symptoms suggestive of infection should be evaluated and treated as high risk

Pneumonia

- Bacterial – community onset, hospital acquired/ Nosocomial
- Opportunistic bacterial infection – Nocardia, rhodococcus
- Fungal infections – invasive mold infections, endemic mycoses
- Mycobacterial infections

Case

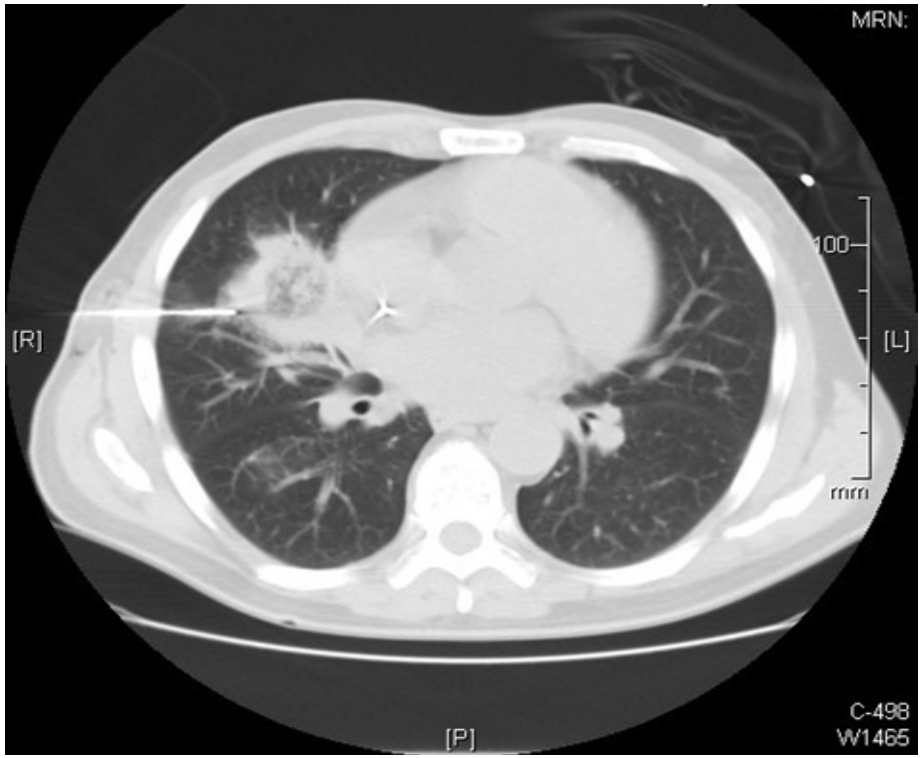
- 62-year-old male with AML, failed induction and re-induction chemotherapy. Currently on Decitabine, and venetoclax. He has been on prophylactic levofloxacin, acyclovir and isavuconazole. He was admitted with fever to 102 F, cough with right sided chest discomfort, and hemoptysis. He had a CT scan of the chest that revealed a consolidation with reverse halo sign in right lung lower lobe. Bronchoscopy with bronchoalveolar lavage was non-diagnostic, had negative fungal markers (serum and BAL fluid – Aspergillus galactomannan, Beta-D-Glucan, Coccidioides serology and antigen). Microbiologic evaluation was negative. He continues to spike on Meropenem.
- Next step:
  - 1. CT guided biopsy vs. cf DNA from blood
  - 2. Empiric antifungal therapy with Echinocandin
  - 3. Empiric therapy with lipid or liposomal amphotericin
  - 4. Posaconazole

Case continued

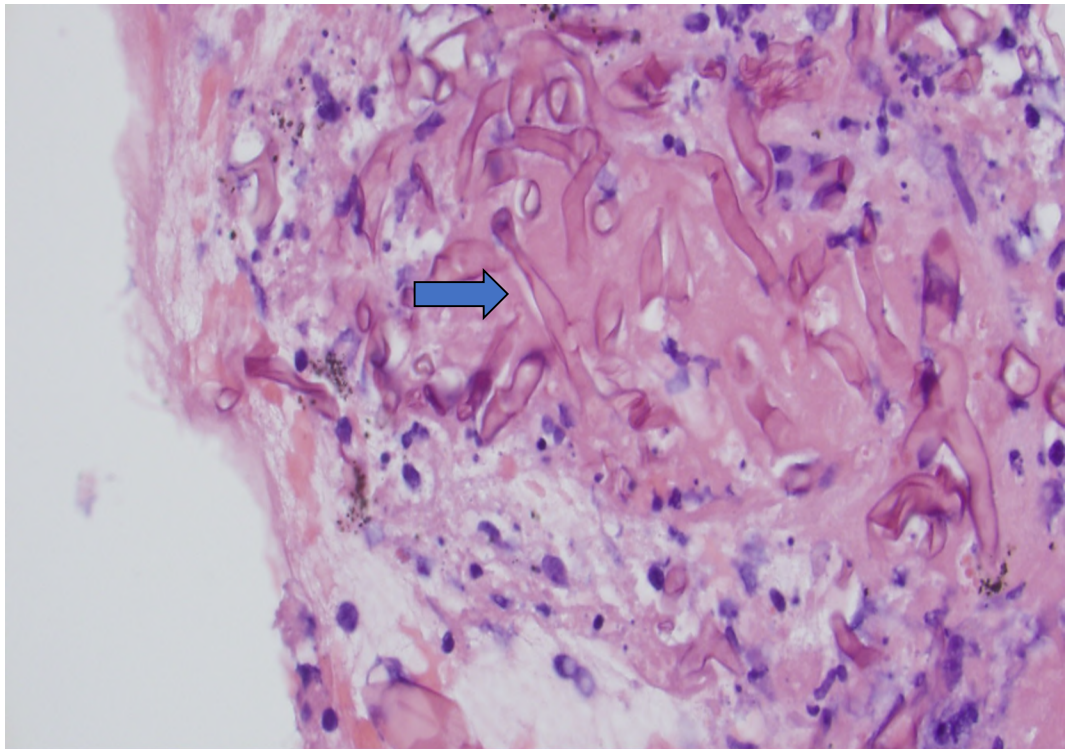
- Patient was switched to Posaconazole, and biopsy held due to severe thrombocytopenia. Patient had low grade intermittent fever on therapy. Vancomycin was added. CT scan done 10 days later shows increase in size of the infiltrate. Infectious Disease consulted.

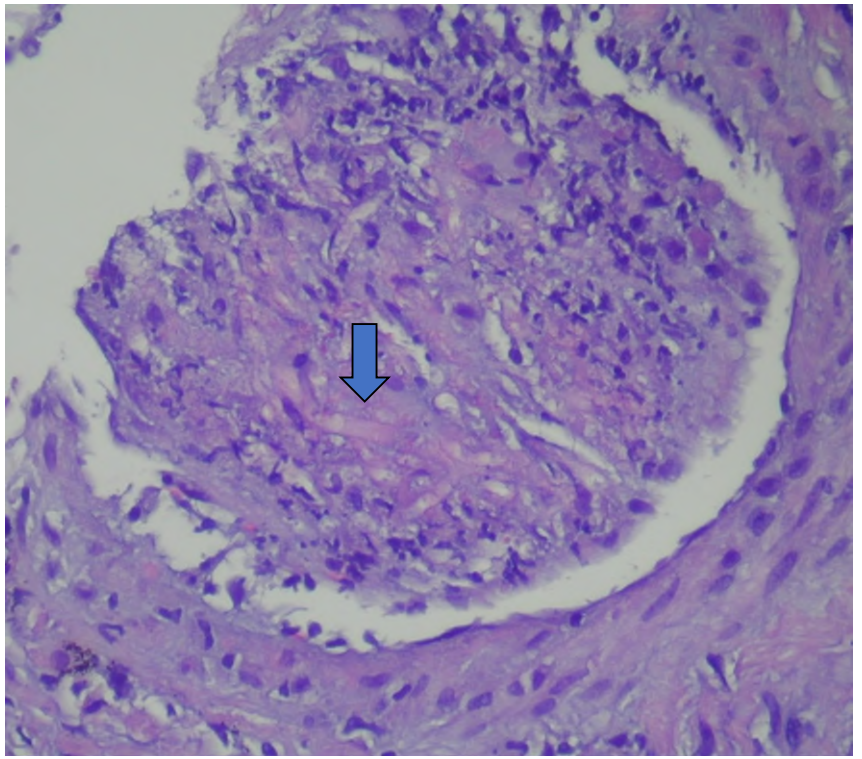
- Next Step:
  - 1. CT guided biopsy of the mass
  - 2. Repeat BAL
  - 3. Change posaconazole to liposomal amphotericin (was on Isavuconazole for 3 months)
  - 4. Add Gentamicin
  - 5. Both choice 1 and 3

Imaging



Pathology





Risk factors of Invasive Mold Infections

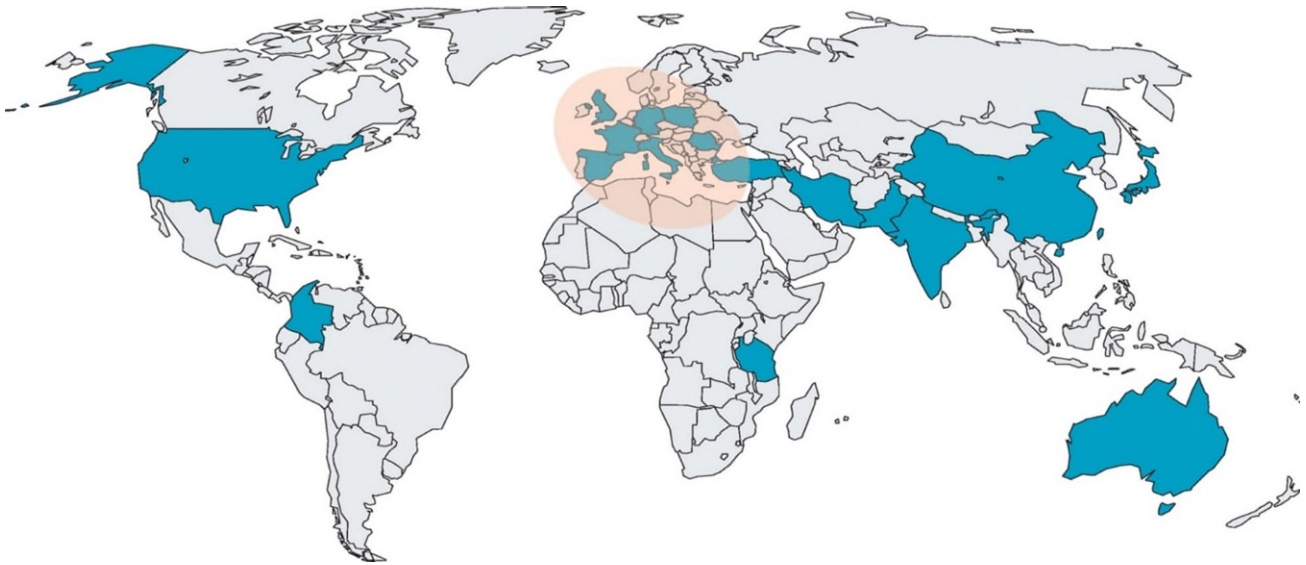
- Prolonged and profound neutropenia (> 1 week) – in the setting of induction chemotherapy for AML
- Use of high dose steroids in ALL
- In CLL Patients – Ibrutinib increases risk for Aspergillosis and dissemination to CNS, especially when also on steroids
- Heavily treated Multiple myeloma patients
- Iron overload
- Uncontrolled hyperglycemia/ diabetes
- Environmental exposures
- In California/ Arizona/ Southwest US – Coccidioides should always be a consideration

Epidemiology of IFI and troubling trends

- Invasive aspergillosis most common (ahead of *Candida spp*.)
- Breakthrough infections with mucormycosis and uncommon molds in those on triazole prophylaxis
- Azole resistant aspergillosis – in context of azole prophylaxis and agricultural use
- Echinocandin resistance in *C. glabrata* and break through infection with *Trichosporon spp.,* and mucormycosis
- Emergence of uncommon mold such as *Fusarium spp., and* Candida auris

Nucci et al. Blood. 2014;124(26):3858-69
Lancet Infect Dis. 2017;17(12)
J Infect Dis. 2017;216:53:s436-44
Girmenia et al. Med Mycol. 2019;57:S127-37

Azole Resistance through TR34/L98H or TR46/Y121F/T289A mutations



Countries where mechanistic resistance is found are shown in blue. The region of highest burden of resistance is marked by the shaded oval (adapted from Verweij et al).

Perlin DS, Rautemaa-Richardson R, Alastruey-Izquierdo A. The global problem of antifungal resistance: prevalence, mechanisms, and management. Lancet Infect Dis. 2017;17(12)

Special considerations

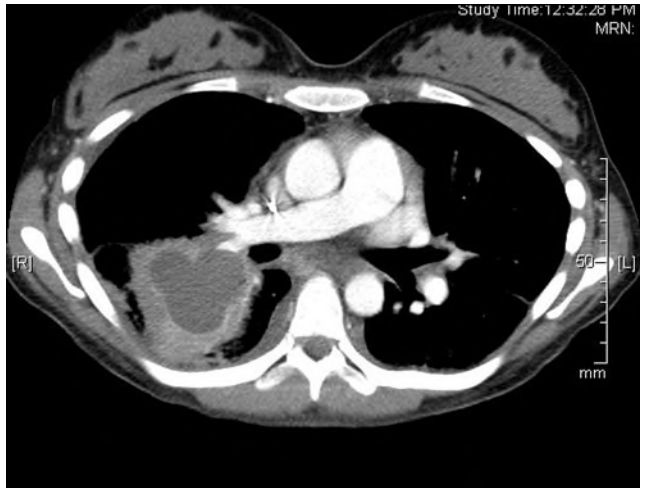
- With yeast fungemia: in the right setting think of cryptococcus, trichosporon.
- Candida glabrata: concern for fluconazole and echinocandin resistance
- Candida lusitaniae: inherently resistant to amphotericin B
- Candida auris: Multi-drug resistant; azoles, echinocandin. On skin, initially described from otitis externa cases. MALDI-TOF accurate identification. If microbiology lab indicates C. haemulonii – need to check for C. auris
- Fungemia requires removal of all hardware/ CVC's

Diagnostic work up

- Depends on the suspected site of infection
- Sino-pulmonary:
  - **Sputum** – usually not present during neutropenic phase
  - **Imaging**
  - **Bronchoscopy with bronchoalveolar lavage** – test for Aspergillus GM/PCR, Mucor PCR, PJP PCR, legionella culture/PCR, routine bacterial/ AFB and fungal cultures, cytology and in appropriate setting M.TB PCR and Nocardia PCR
  - **Biopsy** – CT guided transthoracic needle biopsy, and if non-diagnostic may require open lung biopsy
  - **Sinus biopsy** (not a swab)
  - **Cf DNA by NGS**

- Other sites: CNS, visceral organs, osteoarticular

Imaging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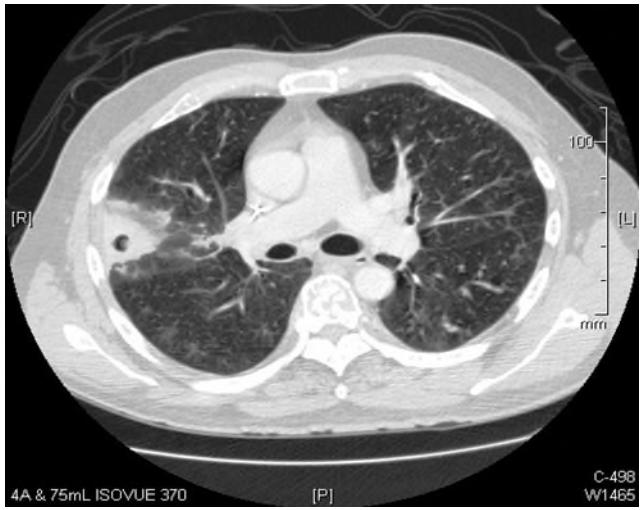
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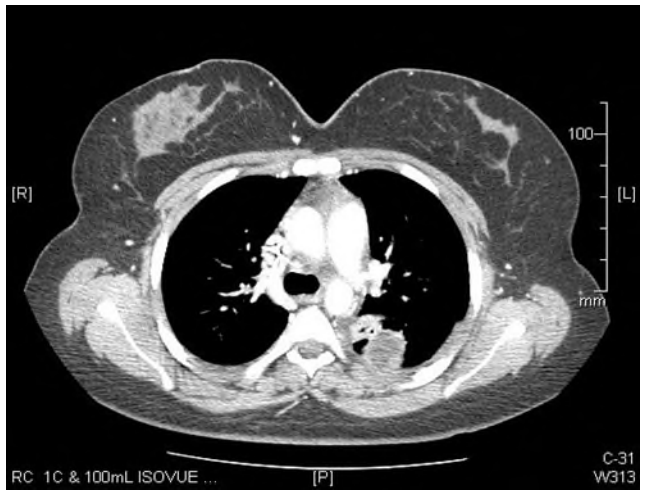
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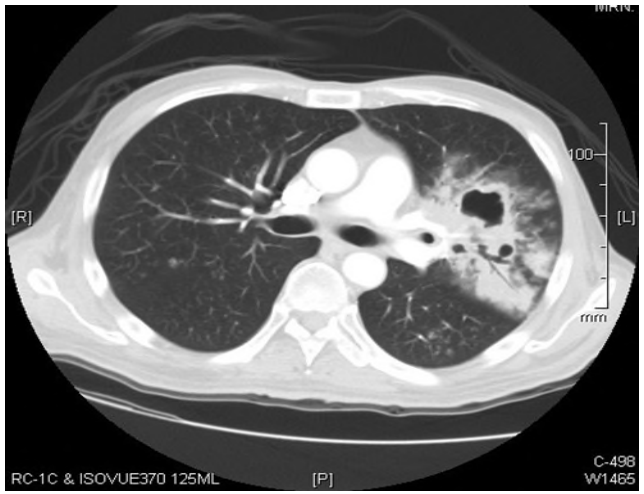
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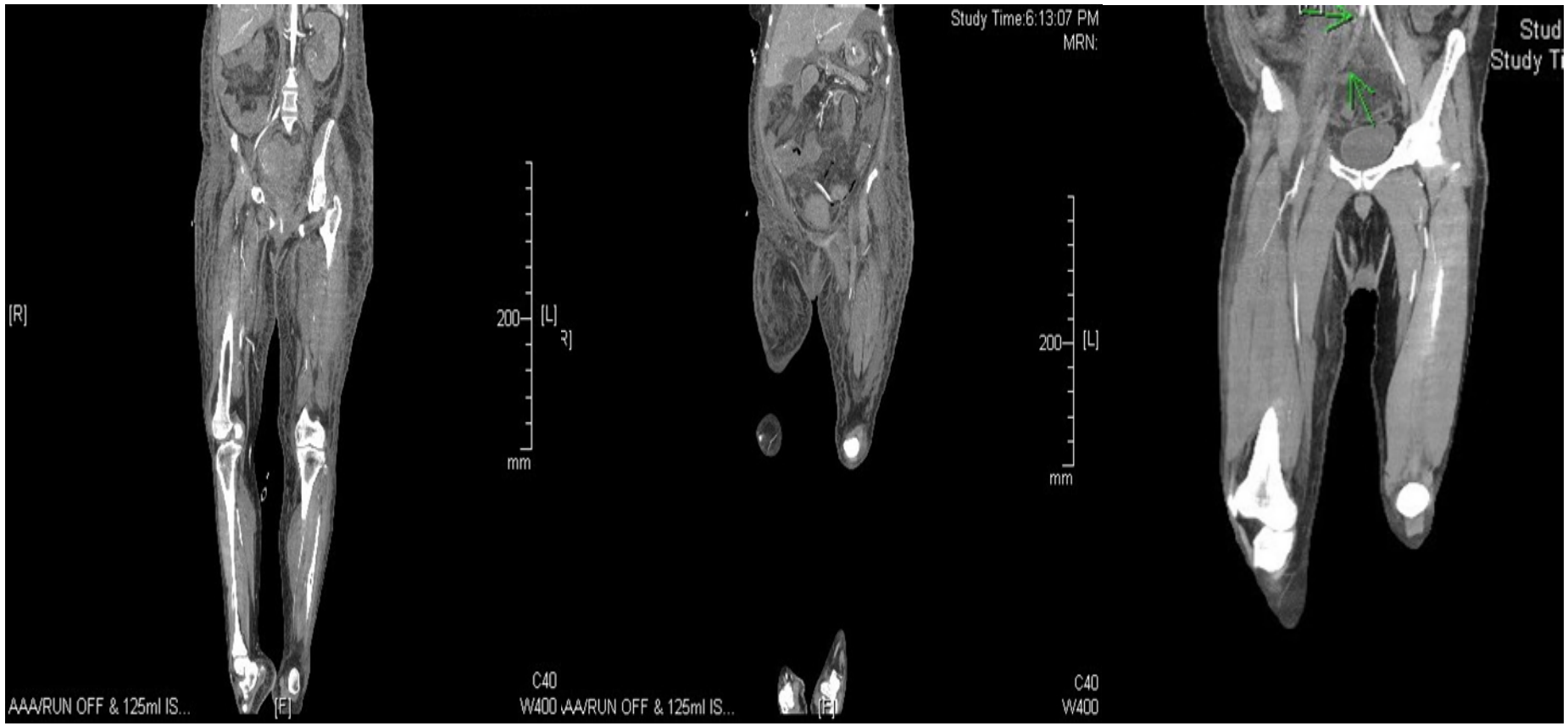
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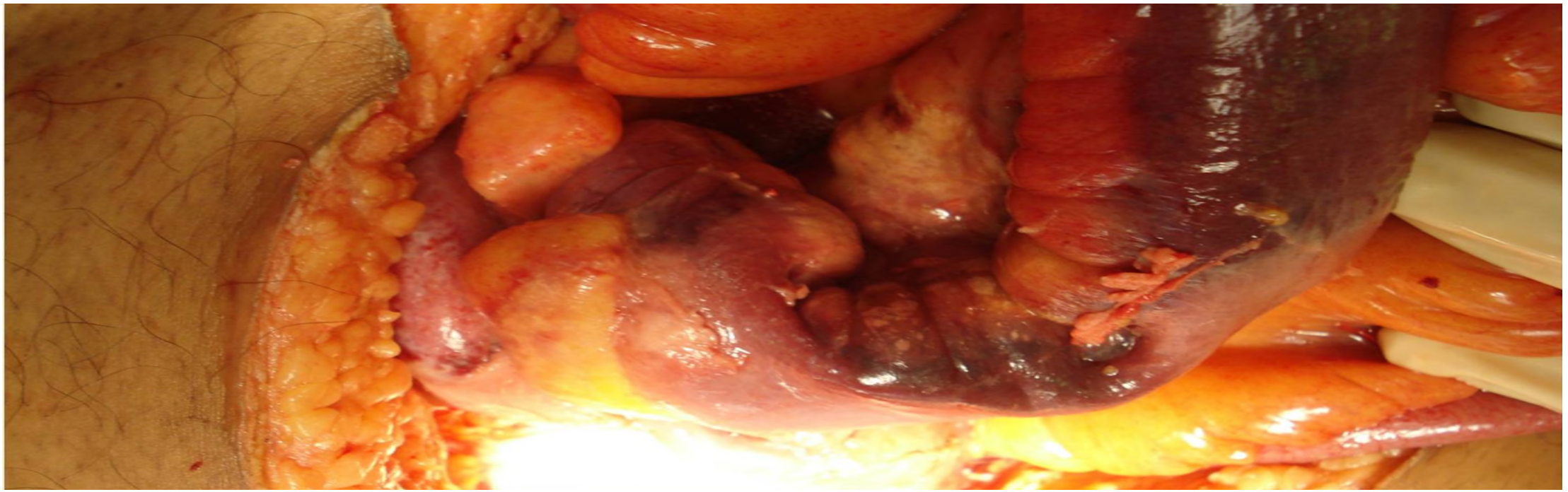
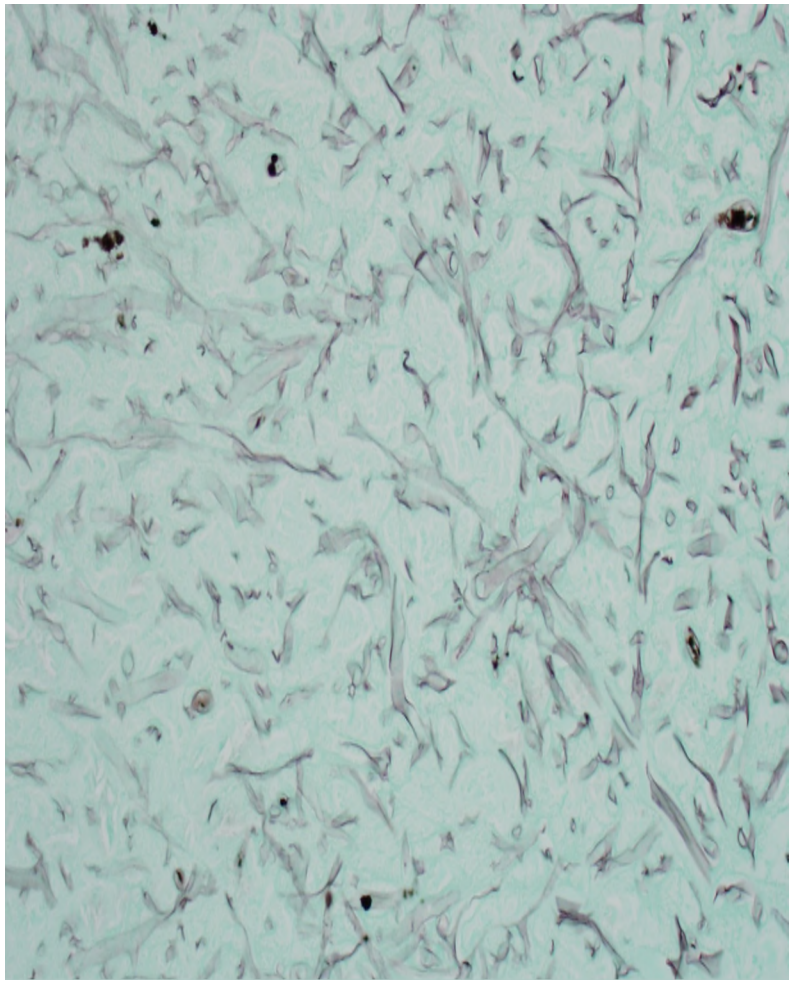
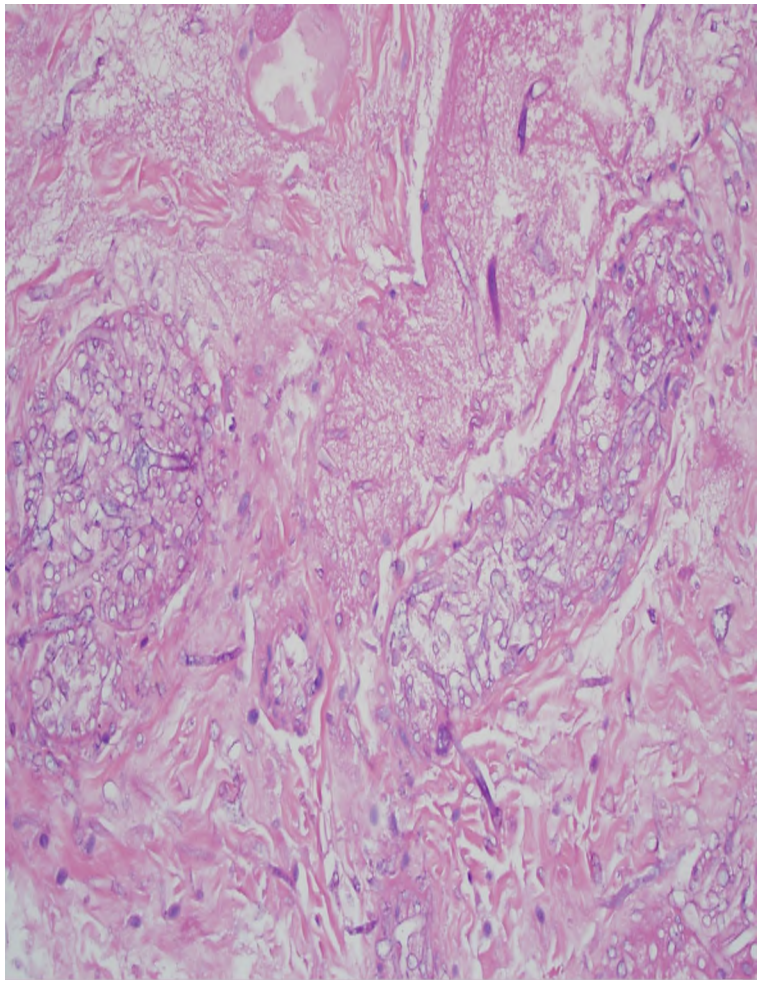






Isavuconazole vs Voriconazole in Invasive Aspergillosis

Endpoint	Isavuconazole	Voriconazole
ITT Pop:		
N	258	258
Mortality	48 (18.6%)	52 (20.2%)
mITT Pop:		
N	143	149
Success Rate	50 (35.0%)	47 (36.4%)

- Secure trial. Maertens et al. Lancet. 2016. 387(10020):760-9

Isavuconazole vs Ampho B-Based Treatment of Mucormycosis

Endpoint	Isavuconazole	Ampho B*
Mortality	7/21 (33.3%)	13/33 (39.4%)
Success	6/19 (31.6%)	

*matched controls from Fungiscope Registry

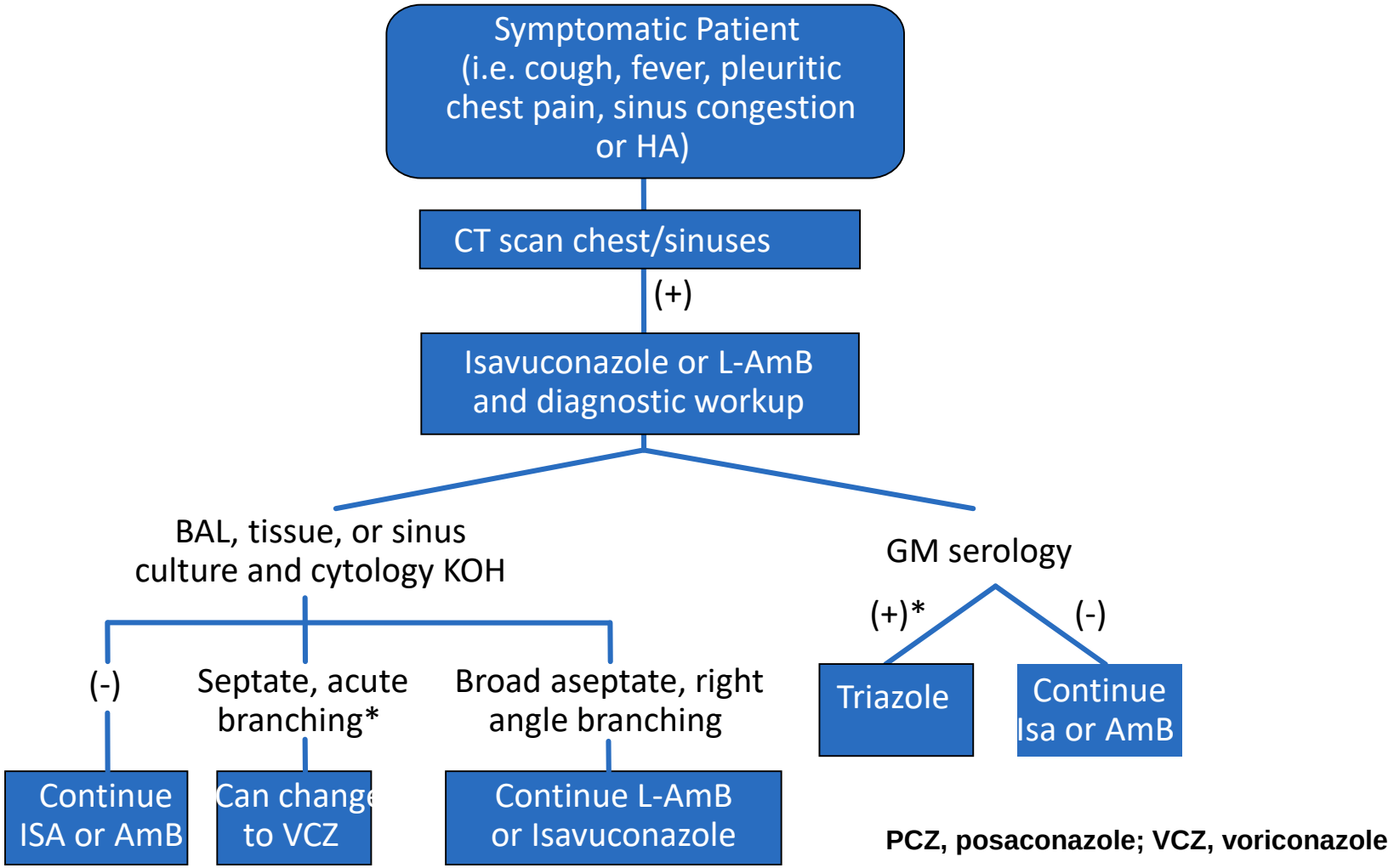
Marty FM et al. Lancet. 2016;16(7):828-37

Role of Combination Therapy: Invasive Aspergillosis

- Generally reserved for mold infections in patients at highest risk for treatment failure
- Important that treatment is for PROVEN OR PROBABLE invasive fungal infection
- Bedside decision
- Consider toxicity and drug interactions

Lewis RE. *Pharmacotherapy.* 2006;26(6 Pt 2):61S-67S.
Marr KA, et al. *Clin Infect Dis.* 2004;39:797-802.

Invasive Mold Infection Algorithm



PCZ, posaconazole; VCZ, voriconazole

*Combination therapy suggested

Combination Antifungal Therapy for Invasive Aspergillosis

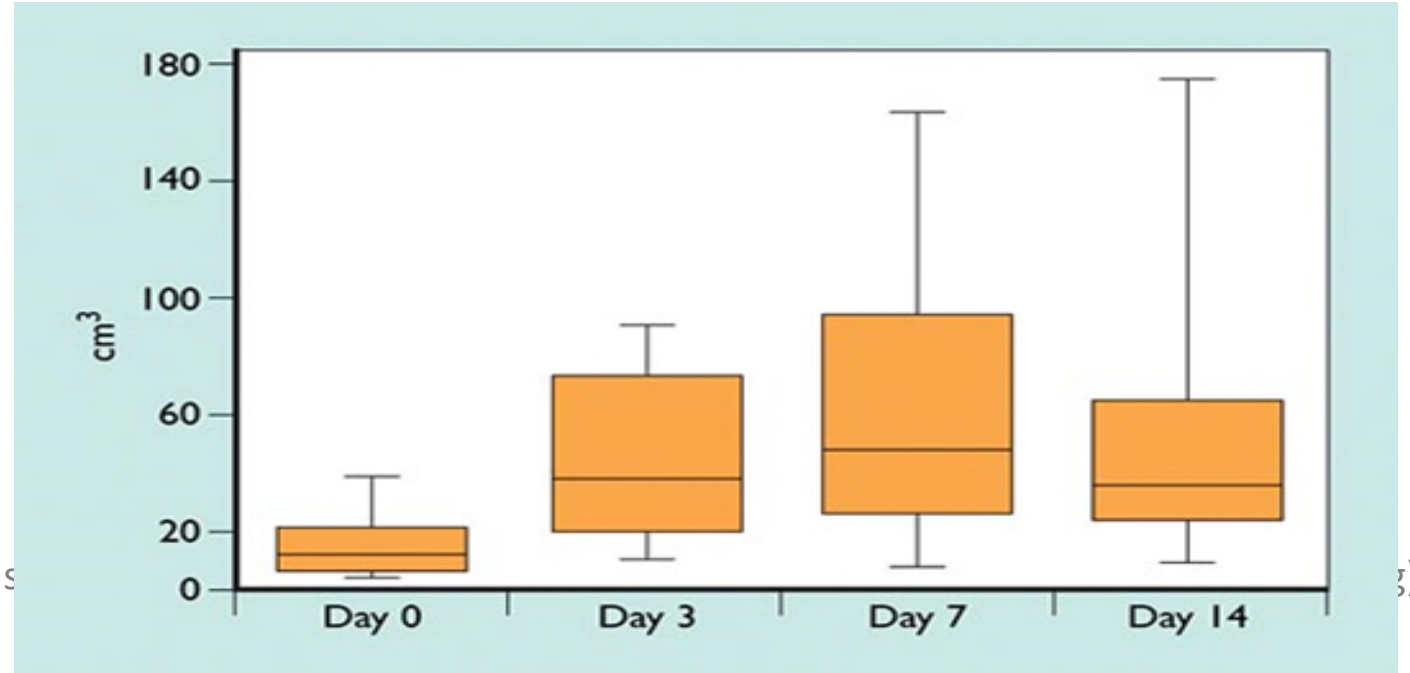
Mortality

Group	Monotherapy (Voriconazole)	Combination (Vori + Anidula)	P value
Overall, 6-week mortality	39/142 (27.5%)	26/135 (19.3%)	0.087
Subgroup* 6-wk mortality	30/110 (27.3%)	17/108 (15.7%)	0.037

*IA diagnosis established by radiographic findings and maximum galactomannan positivity.

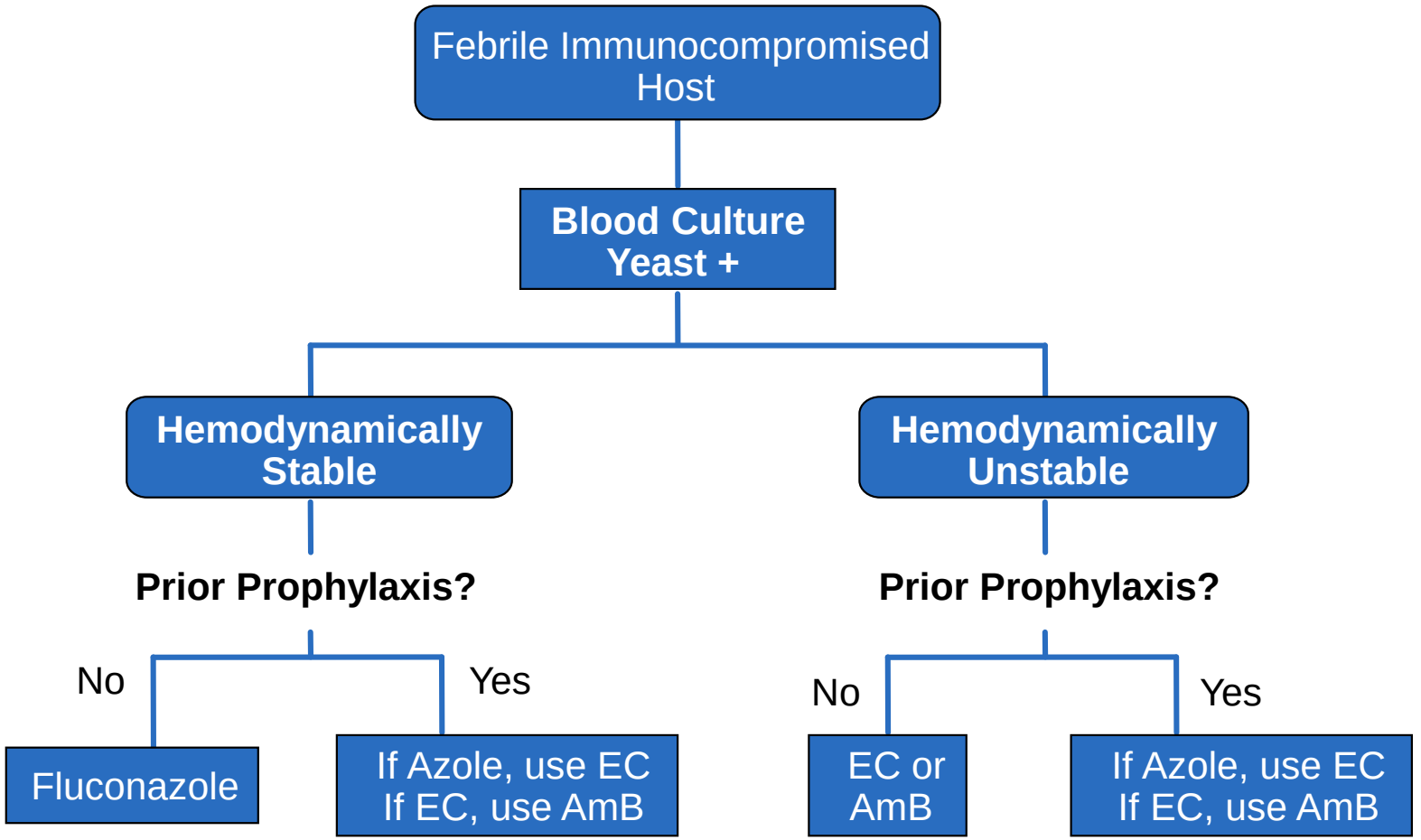
Marr KA et al. *Ann Intern Med 2015; 162:81-89.*

Treatment effect on follow up imaging



- Follow up imaging s g) – Calliot et al.

Invasive Candidiasis Algorithm



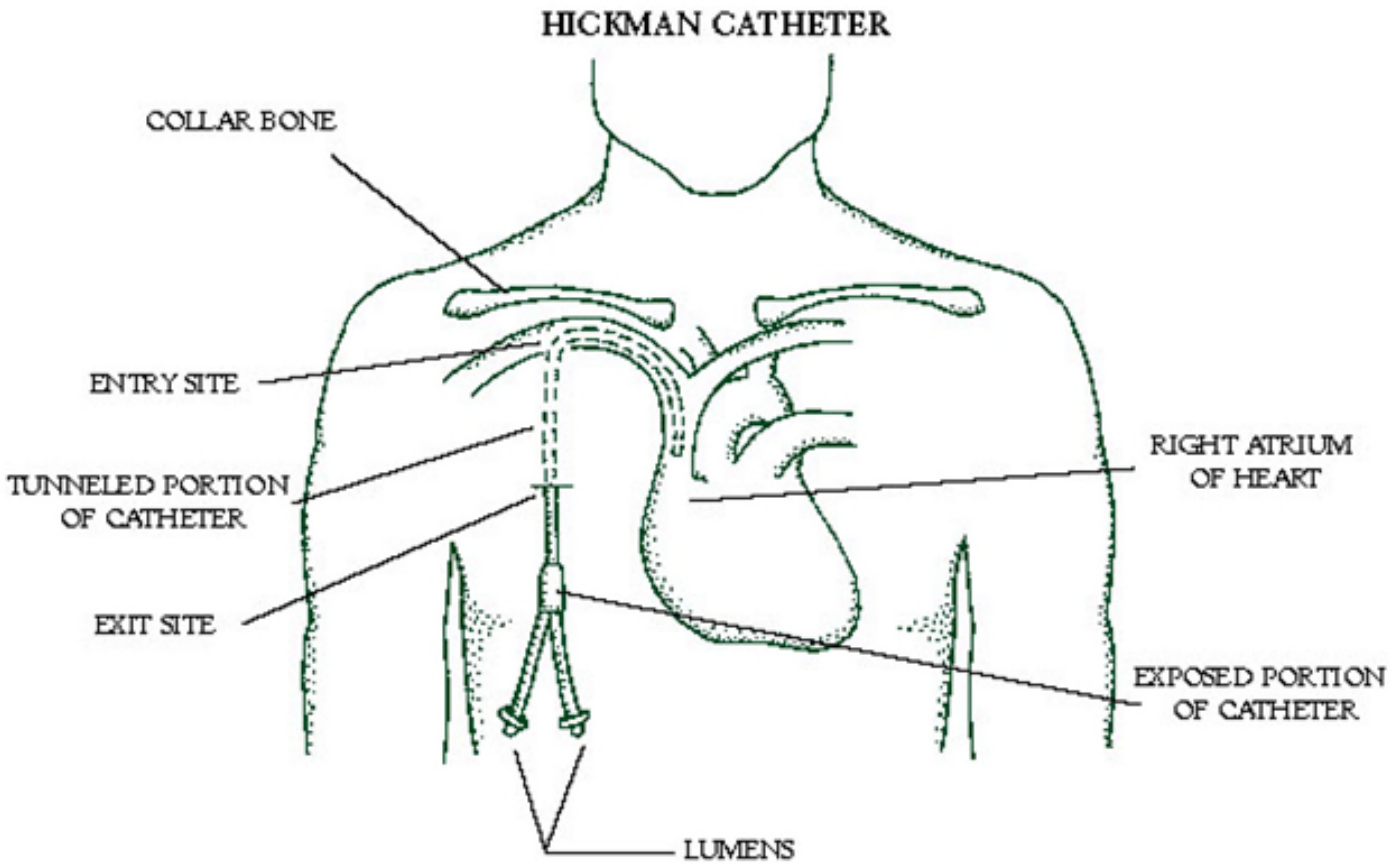
EC: echinocandin, AmB: Amphotericin B

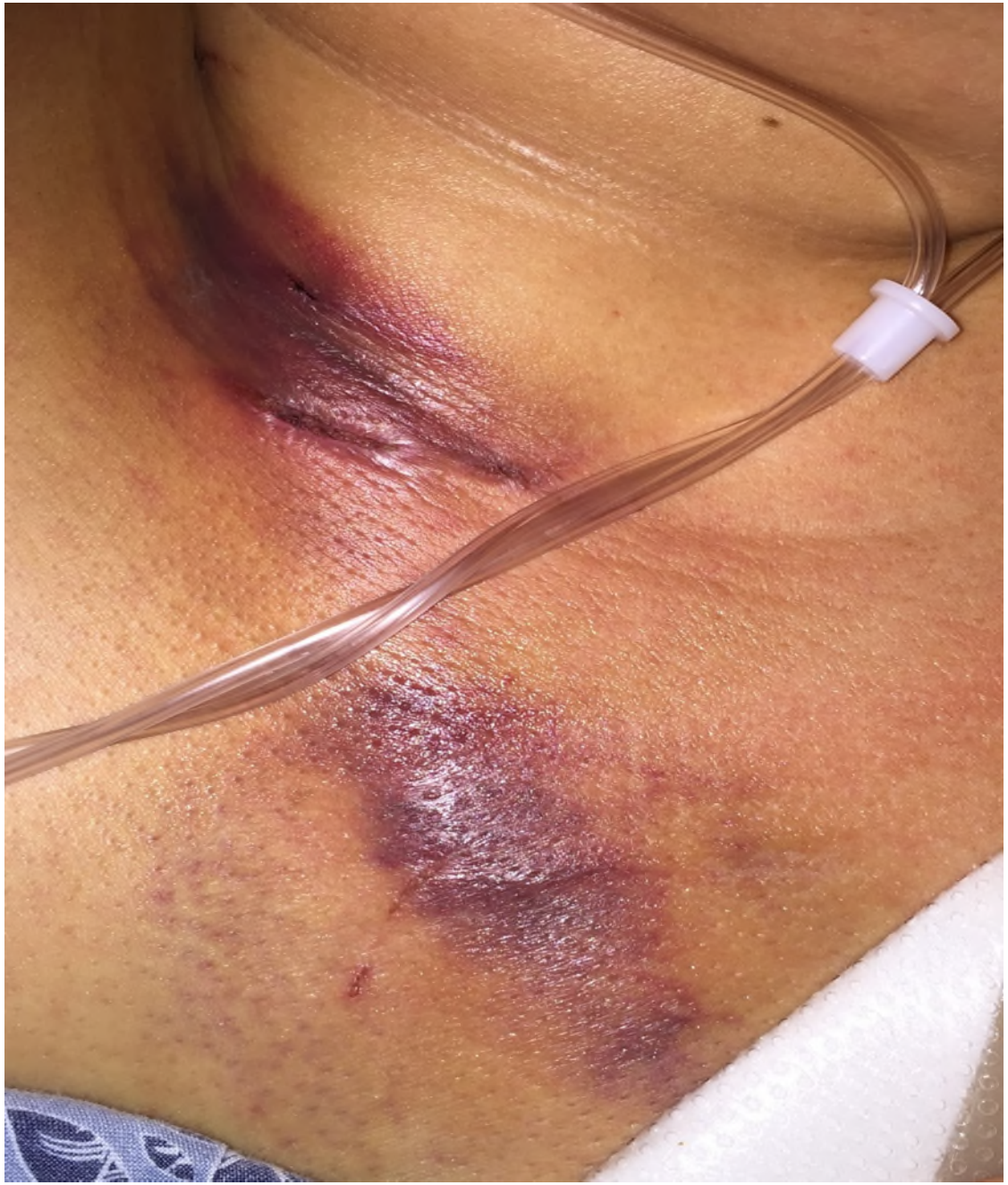
Ito JI, et al. *Leuk Lymph* 2010;51:1623–31

Central venous catheter related infections

- Tunneled catheters – Hickman/ Broviac (exit site infection vs. tunnel infection)
- PICC (exit site infection/ cellulitis)
- Port-a-Cath (pocket/ tunnel infection)
- All of the above can be associated with DVT/ septic thrombophlebitis

Dual Lumen RAC





Catheter related infection
Need for CVC removal

- **Exit site infection**
  - Can be treated without removing catheter.
- **Pocket space/ tunnel infection**
  - Will always require removal.
- **Should be removed if the following organisms are isolated:**
  - *Candida* sp., *Fusarium* sp.
  - *Corynebacterium JK, Bacillus species*
  - Mycobacterium (esp. *M fortuitum, M chelonae*)
  - *Pseudomonas aeruginosa*
  - *Staphlococcus aureus* (including MRSA)
  - Enterococci (esp. VRE)
- **Or pt has one of the following:**
  - Septic thrombophlebitis
  - Septic emboli
  - Persistent bacteremia or fevers
  - Endocarditis
  - Pocket-space abscess (in PAC pocket)

Catheter related infection

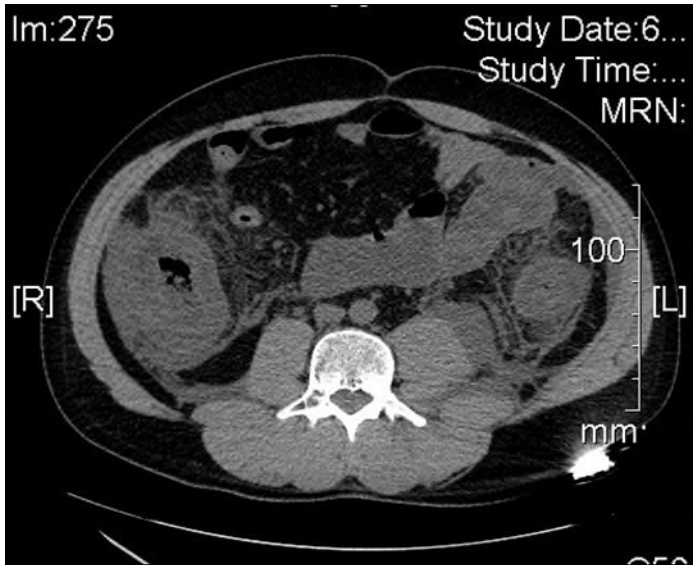
- Duration of antibiotics:
    - Uncomplicated infection: 14 days
- Complicated infections such as deep tissue infection, endocarditis, septic emboli, septic thrombophlebitis, or persistent fungemia or bacteremia occurring >72 hr. after removal of catheter: 4-6 weeks

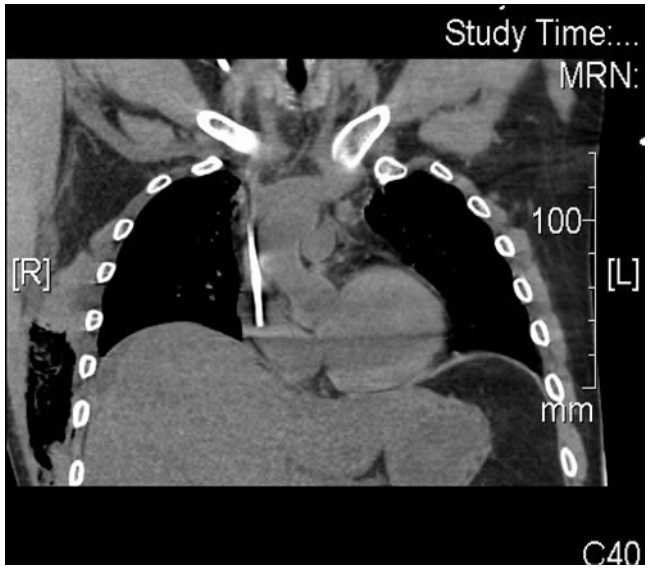
Gastrointestinal Infections

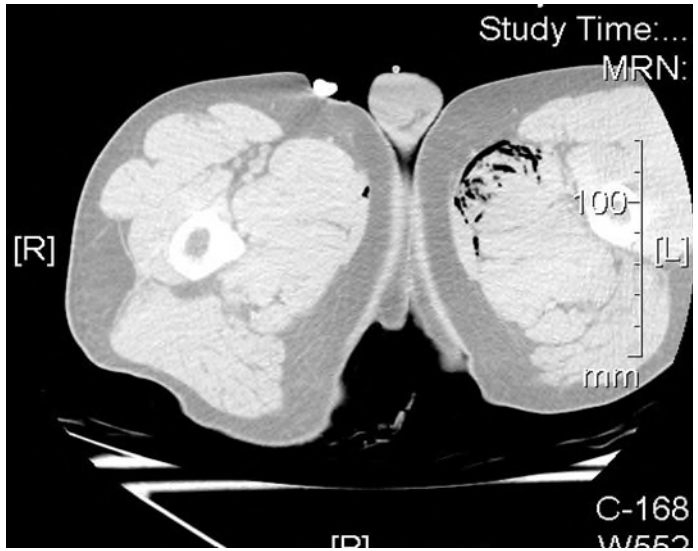
Diarrhea

- Mucositis from induction chemotherapy
- Neutropenic enterocolitis/ Typhlitis: abdominal pain and tenderness is hallmark – imaging and clinical diagnosis
- Clostridium difficile colitis – PCR/GDH/EIA for toxin
- Enteric viruses – Stool biofire panel
- Reactivation of parasite, e.g., strongyloidiasis – stool for O/P, duodenal aspirate on UGI endoscopy with biopsies
- Non-Infectious causes
- Drug induced – often chemotherapeutic agents
- In elderly or those with atherosclerotic vascular disease – mesenteric ischemia – imaging and clinical diagnosis

Typhlitis with Clostridial Myonecrosis



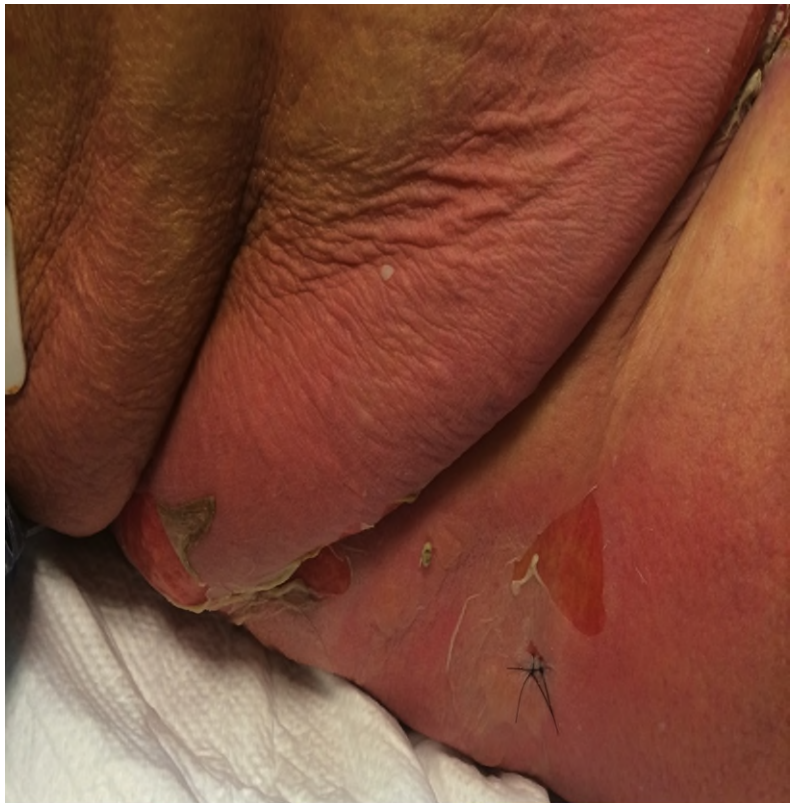


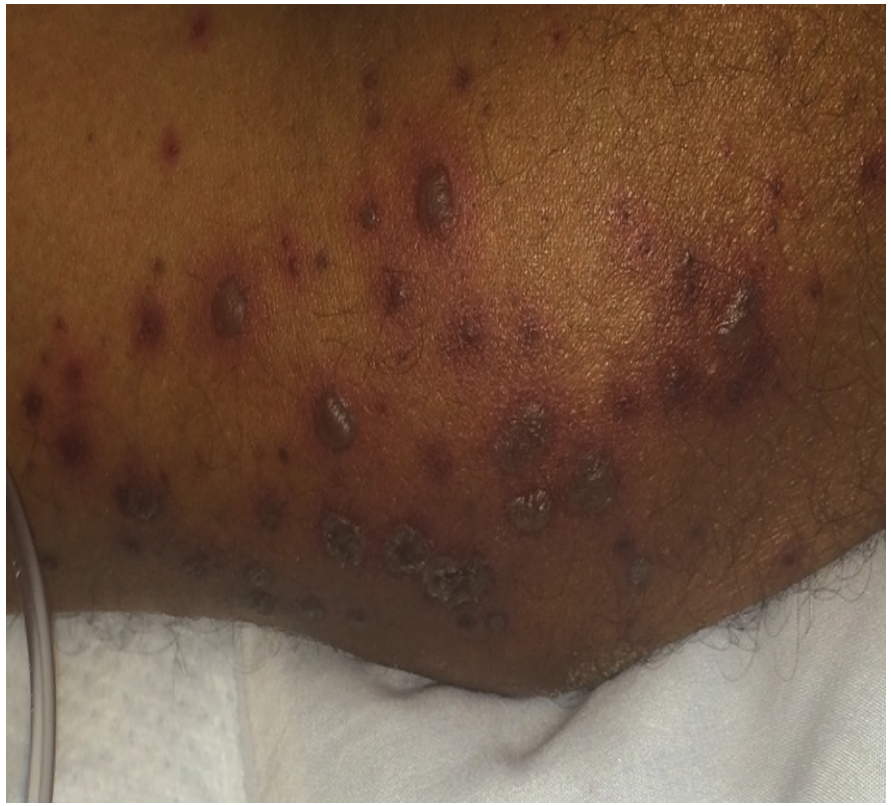


Dermatologic

- **Drugs:** antibiotics, allopurinol, chemotherapy, Dilantin, etc.
- **Viral exanthem** – CMV (suspect in lymphoid malignancies/ advanced myeloma – has been noted with Ixazomib), Enteroviruses, Parvovirus B19.
- **Vesicular rash:** HSV, VZV, Enteroviruses
- **Bacterial** – may present with ecthyma gangrenosum, folliculitis, cellulitis, & necrotizing fasciitis (severe pain but signs may be minimal – surgical emergency). Streptococcal/ staphylococcal, pseudomonas, nocardia (cold abscesses), atypical mycobacteria
- **Fungal:** subcutaneous painless or painful nodules with or without necrosis: aspergillus, fusarium, scedosporium, acremonium, Mucorales
- **Non-infectious:** sweet syndrome, pyoderma gangrenosum, drug induced – often have fever
- **Evaluation:** punch biopsy, blood cultures, and for vesicles – scrape and send for viral cultures, VZV and HSV DFA/ PCR

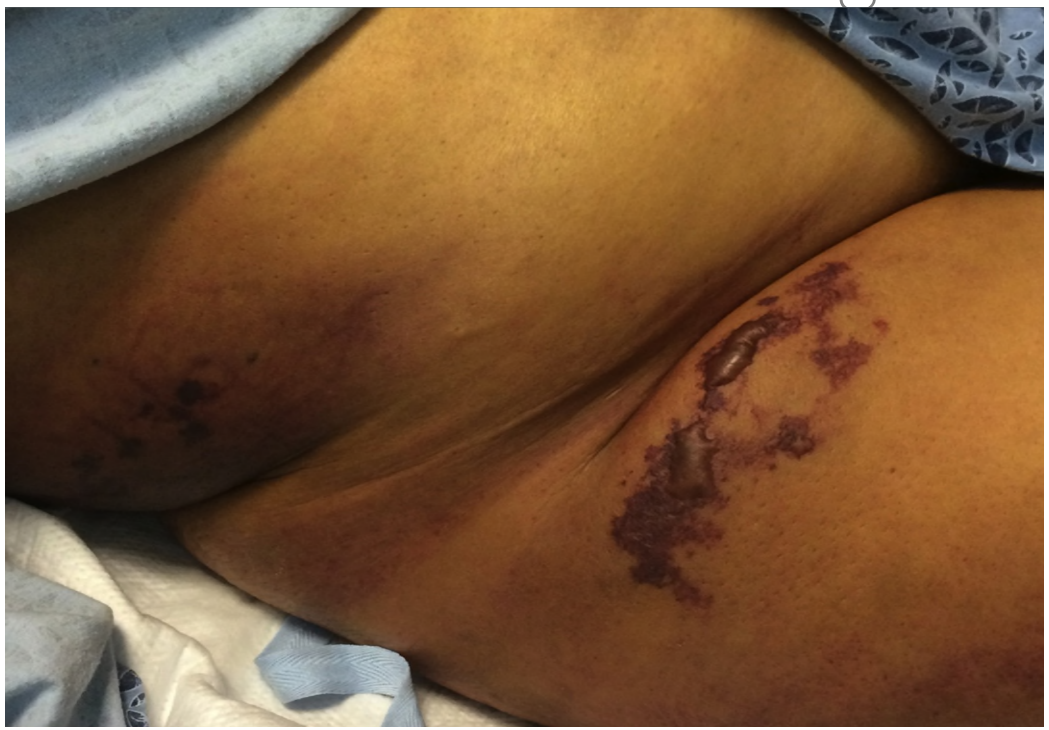
Non-Infectious

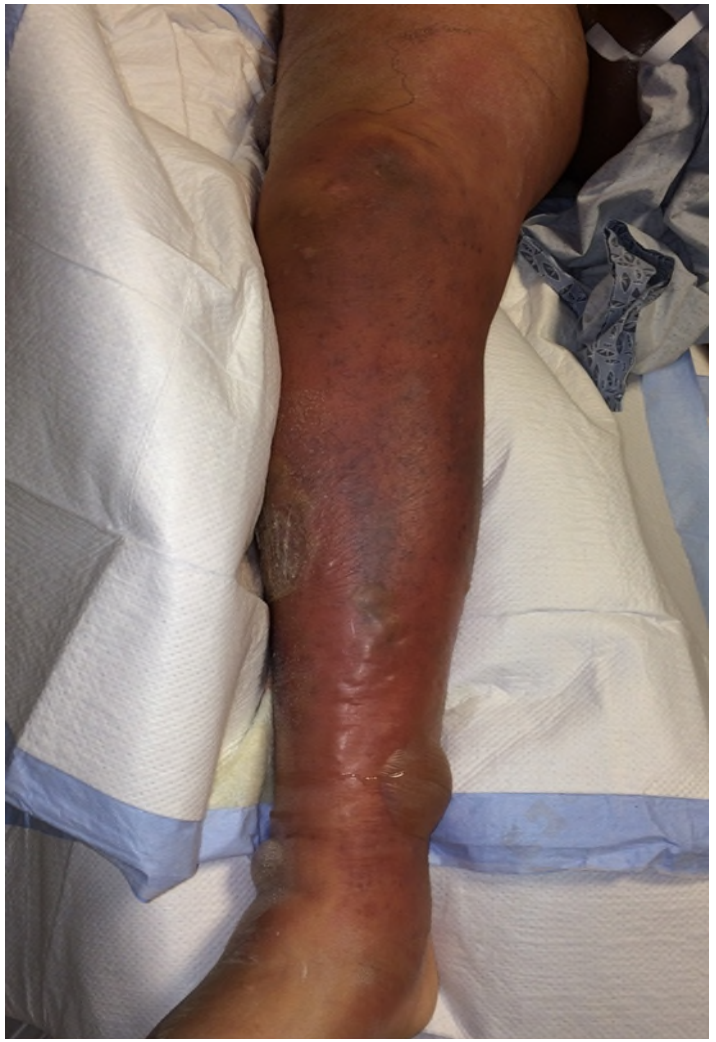




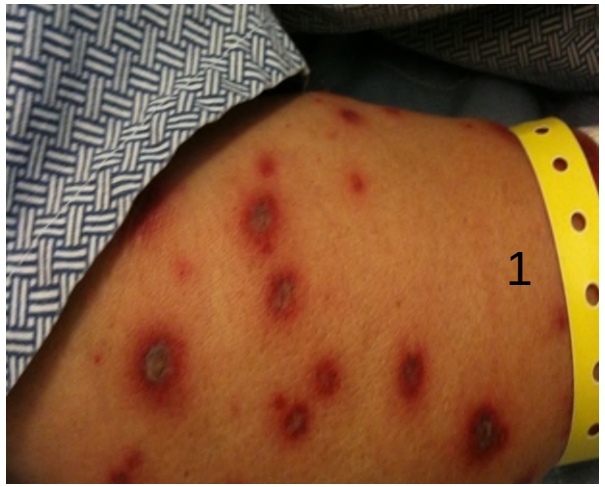
Steven Johnsons

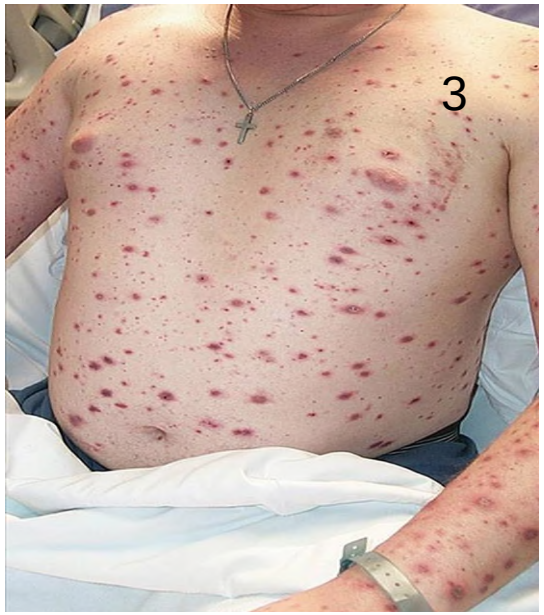
Necrotizing Fasciitis

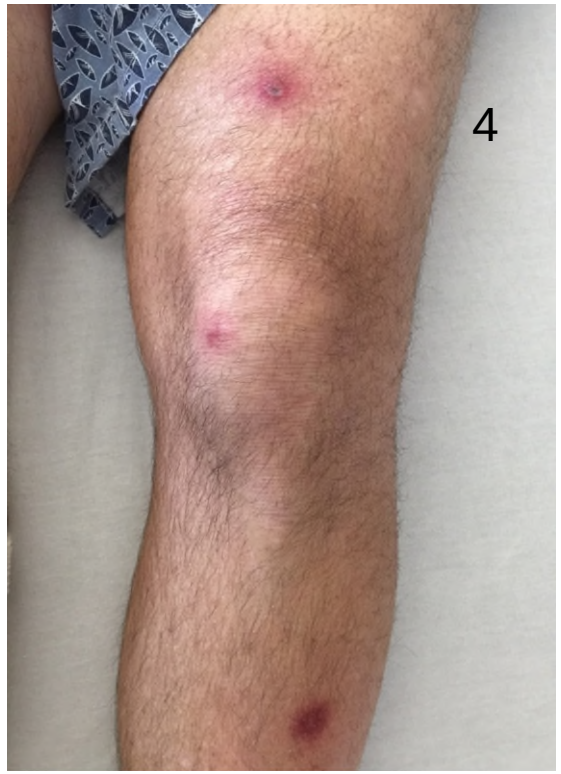


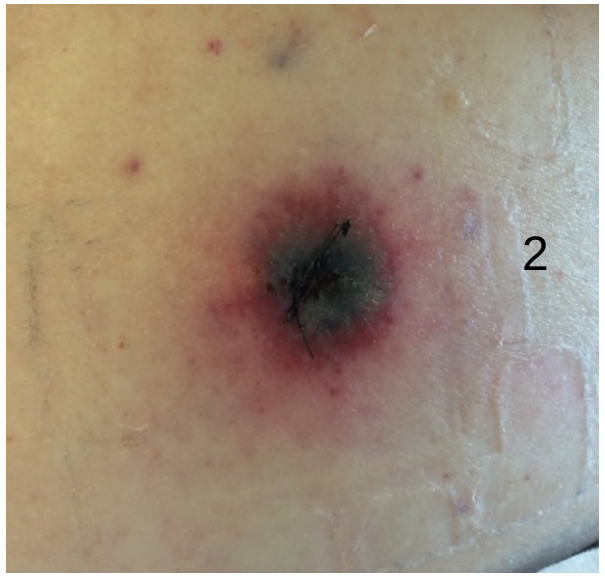


Fungal Lesions









1. Acremonium
2. Mucor

3 & 4. Fusarium

Last case

- 38-year-old male with recently diagnosed Hodgkin's disease is planned to begin Rituximab and CHOP regimen. He was born in Southeast Asia and moved with family to United states when he was 10 years old. His mother was diagnosed with end stage liver disease and cirrhosis secondary to HBV. Which of the following test if positive can be helpful prevent fulminant liver failure by instituting antiviral prophylaxis.

1. Hepatitis C antibody
2. Hepatitis B surface antibody
3. Hepatitis B core antibody total (HBcAb)
4. Hepatitis B surface antigen (HBsAg)
5. Either of 3 or 4

Thank you