Neutropenic Fever

www.idsociety.org

CID 2011; 52 (4):e56-e93

www.nccn.org

Prevention and Treatment of Cancer-Related Infections

Definitions

- Fever:
  - Single oral temperature of ≥ 101°F (38.3°C)
  - Temperature ≥ 100.4°F (38.0°C) over 1 hour
- Neutropenia:
  - ANC < 500 cells/mm^3
  - Expected ANC < 500 cells/mm^3 within the next 48 hours

65M with AML develops acute fever to 38.5^{0}C 7 days after completing induction chemotherapy. His peripheral blood WBC count is 1 (x10^{3}/mm^{3}) and differential with 50% neutrophils. What is his ANC?

A 5

B 50

C 500

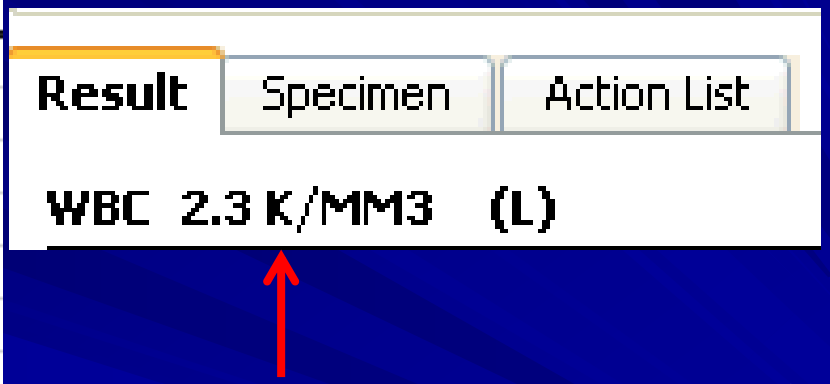
D 5000

E 50%

Calculating ANC

2.3 x 1000 = 2300 x 0.81 = 1863

WBC	2.3 L
RBC	2.87 L
HGB	8.3 L
HCT	26.9 L
MCV	94
MCH	28.9
MCHC	30.9 L
RDW-CV	19.6 H
RDW-SD	67.0 H
Platelet	174
MPV	12.0
telet Estimate	Normal
f Type	SCAN
Immature Granulocyte % (IG%)	2.2 * H
Immature Granulocyte # (IG#)	0.0
Segs	81



Chemotherapy Induced Neutropenia

Relationship Between Neutrophil Count and Infection

- Risk of infection increases as the absolute neutrophil count falls below 1000/mm^3
- Risk of infection is related to
  - degree or depth of neutropenia
  - duration of neutropenia
  - rate at which neutropenia occurs

Severe neutropenia ANC < 100

Bodey et al. *Ann Intern Med.* 1966;64:328-340.

Which of the following cancers has the highest risk of developing neutropenic fever during their course of chemotherapy?

A Breast
B Lymphoma
C Acute leukemia
D Both B & C
E They all have the same risk

Overall Infection Risk in Patients with Cancer[a]	Disease/Therapy Examples	Fever & Neutropenia Risk (See FEV-2)	Antimicrobial Prophylaxis[d]
Low	• Standard chemotherapy regimens for most solid tumors • Anticipated neutropenia less than 7 d	Incidence low	• Bacterial - None • Fungal - None • Viral - None unless prior HSV episode
Intermediate	• Autologous HCT • Lymphoma[c] • Multiple myeloma[c] • CLL[c] • Purine analog therapy (ie, fludarabine, clofarabine, nelarabine, cladribine) • Anticipated neutropenia 7–10 d	Incidence usually high, significant variability may exist	• Bacterial - Consider fluoroquinolone prophylaxis during neutropenia[e] • Fungal - Consider prophylaxis during neutropenia and for anticipated mucositis (See INF-2); consider PCP prophylaxis (See INF-6) • Viral - During neutropenia and longer depending on risk (See INF-3, INF-4, INF-5)
High[b]	• Allogeneic HCT including cord blood • Acute leukemia ▸ Induction ▸ Consolidation/maintenance • Alemtuzumab therapy • GVHD treated with high-dose steroids (>20 mg daily) • Anticipated neutropenia greater than 10 d	Incidence usually high, significant variability may exist	• Bacterial - Consider fluoroquinolone prophylaxis during neutropenia[e] • Fungal - Consider prophylaxis during neutropenia (See INF-2); consider PCP prophylaxis (See INF-6) • Viral - During neutropenia and longer depending on risk (See INF-3, INF-4, INF-5)

NCCN Guidelines V 1.2019 Prevention and Treatment of Cancer-Related Infections

Classification

- Initial neutropenic fever
  - Typically coincides with neutrophil nadir
  - Standard protocol – concern for bacterial infection
- Persistent neutropenic fever
  - Fever despite 4-7 days of empiric antibiotic therapy
  - Complex management – concern for fungal infection
- Recrudescent neutropenic fever
  - Fever that recurs following initial response
  - Wide differential

65M with AML admitted for induction chemo. PICC line placed on admission. Develops neutropenia on HD#12 and fever to 38.6^{0}C on HD#15. Patient notes some chills but no other complaints. Exam unremarkable other than P108. CXR negative. Blood cultures performed and come back positive for *Pseudomonas*. What is the most likely source for his infection?

A Translocation

B PICC line

C Pneumonia

D Urinary tract

E Intra-abdominal abscess

Etiology / Microbiology

Infectious (~20%)

- ***Bacterial translocation***
  - Intestinal
  - Oropharyngeal
- Community-acquired
  - Respiratory viruses
- Healthcare-associated
  - MDR organisms, C.diff
  - CLABSI, CAUTI
- Opportunistic
  - Herpes virus reactivation
  - Fungal

Non-infectious

- Underlying malignancy
- Blood products
- Tumor lysis
- Hematoma
- Thrombosis
- Phlebitis
- Atelectasis
- Viscus obstruction
- Drug fever
- Myeloid reconstitution

Clinical Evaluation

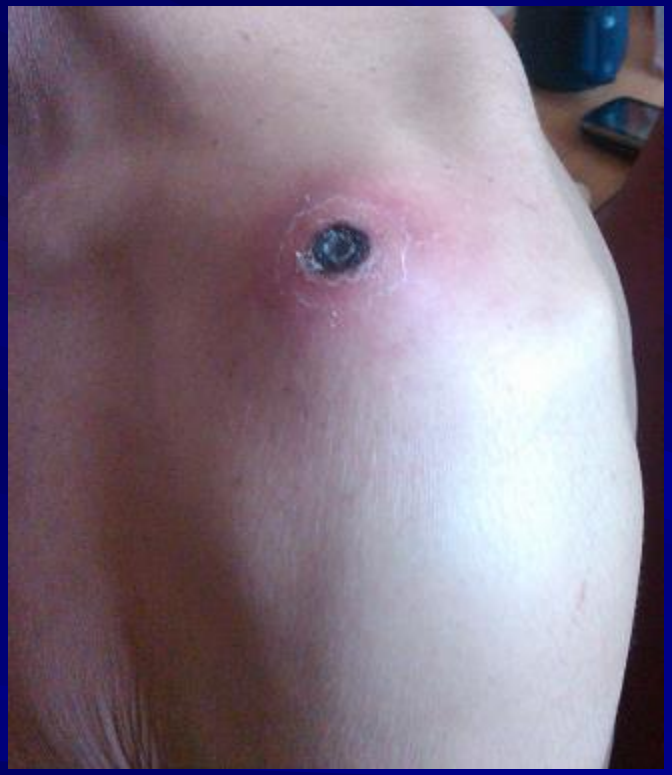
- Symptoms and signs of inflammation may be minimal or absent in the severely neutropenic patient
  - Cellulitis with minimal to no erythema
  - Pulmonary infection without discernable infiltrate on radiograph
  - Meningitis without pleocytosis in the CSF
  - Urinary tract infection without pyuria
  - Peritonitis - abdominal pain without fever or guarding

Sickles, Arch Intern Med 1975; 135;715-9

The Work Up

- Physical Exam:
  - Periodontium
  - Palate
  - Lung
  - Abdomen
  - Perineum
  - Skin
  - Tissue around the nails
  - BM biopsy site
- Blood cultures x2
- Consider CXR & UA
- Targeted workup
  - Urine cx
  - C.diff
  - Exit site cultures
  - Catheter tip cultures
  - CT chest
  - CT abdomen/pelvis
  - NP swab (resp virus)

Ecthyma Gangrenosum



Bacteria:

Pseudomonas

GNR

Staphylococcus aureus

Fungus:

Aspergillus

Fusarium

65M with AML admitted for induction chemo. PICC line placed on admission. Develops neutropenia on HD#12 and fever to 38.6^{0}C on HD#15. Patient notes some chills but no other complaints. No recent antibiotic use. Exam unremarkable other than P108. CXR negative. Blood cultures performed. Next best step in management?

A Observe off antibiotics

B Start levofloxacin

C Start cefepime

D Start vanco + cefepime

E Start vanco + cefepime + gent

Initial Neutropenic Fever

- Empiric antibiotics:
  - *Pseudomonas* and *Streptococcus* coverage
    - INPT: Cefepime OR Zosyn OR Meropenem
      - +/- Aminoglycoside (severe sepsis, significant risk for resistance)
      - +/- Vancomycin
    - OUTPT: Augmentin + Cipro
- Bacterial etiology:
  - Gram-negative organisms
    - *Pseudomonas aeruginosa*, *E. coli*, *Klebsiella*
  - Gram-positive organisms
    - Coag neg *Staph,* Viridans *Streptococcus,* MRSA *Corynebacterium jeikeium*

Empiric Vancomycin

10. Vancomycin (or other agents active against aerobic gram-positive cocci) is not recommended as a standard part of the initial antibiotic regimen for fever and neutropenia (A-I). These agents should be considered for specific clinical indications, including suspected catheter-related infection, skin or soft-tissue infection, pneumonia, or hemodynamic instability.

Randomized trials comparing regimens with and without vancomycin for empiric therapy of initial neutropenic fever - no mortality benefit, no reduction in duration of fever.

Empiric Vancomycin

- Hemodynamic instability or other evidence of severe sepsis
- ~~Pneumonia documented radiographically~~
- Positive blood culture for gram-positive bacteria, before final identification and susceptibility testing is available
- Clinically suspected serious catheter-related infection (eg, chills or rigors with infusion through catheter and cellulitis around the catheter entry/exit site)
- Skin or soft-tissue infection at any site
- Colonization with methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant enterococcus, or penicillin-resistant *Streptococcus pneumoniae* (see text)
- Severe mucositis, if fluoroquinolone prophylaxis has been given and ceftazidime is employed as empirical therapy

65M with AML admitted for induction chemo. PICC line placed on admission. HD#12 neutropenia.

HD#15 Tm 38.6^{0}C. Exam: P108, lethargic/confused. CXR negative. Patient started on vanco + cefepime + gent. HD#17 still febrile 38.3^{0}C x 2d, but mental status back to baseline. D15 and D16 BCxs remain negative.

Next best step in management?

A Stop vanco

B Change cefepime to imipenem

C Switch to linezolid, imipenem, tobra

D Add micafungin

E Continue current regimen

Antimicrobial Modification

18. If vancomycin or other coverage for gram-positive organisms was started initially, it may be stopped after 2 days if there is no evidence for a gram-positive infection (A-II).

Vancomycin can cause nephrotoxicity especially with trough levels > 15.
Synergistic nephrotoxicity with vancomycin in combination with aminoglycosides.

65M AML admit for induction chemo. PICC line placed. HD#12 neutropenia. HD#15 Tm 38.6^{0}C. Exam: P108, lethargic/confused. CXR negative. Patient started on vanco + cefepime + gent. HD#17 still febrile 38.3^{0}C x 2d, but MS back to baseline. D15 BCxs positive for pan-sensitive E.coli (2 of 2 sets + at same time). D16 BCxs negative.

Next best step in management?

A Continue current regimen

B Switch current regimen to ceftriaxone

C D/C vanco, continue cefepime and gent

D D/C vanco and gent, continue cefepime

E Pull PICC line, continue cefepime only

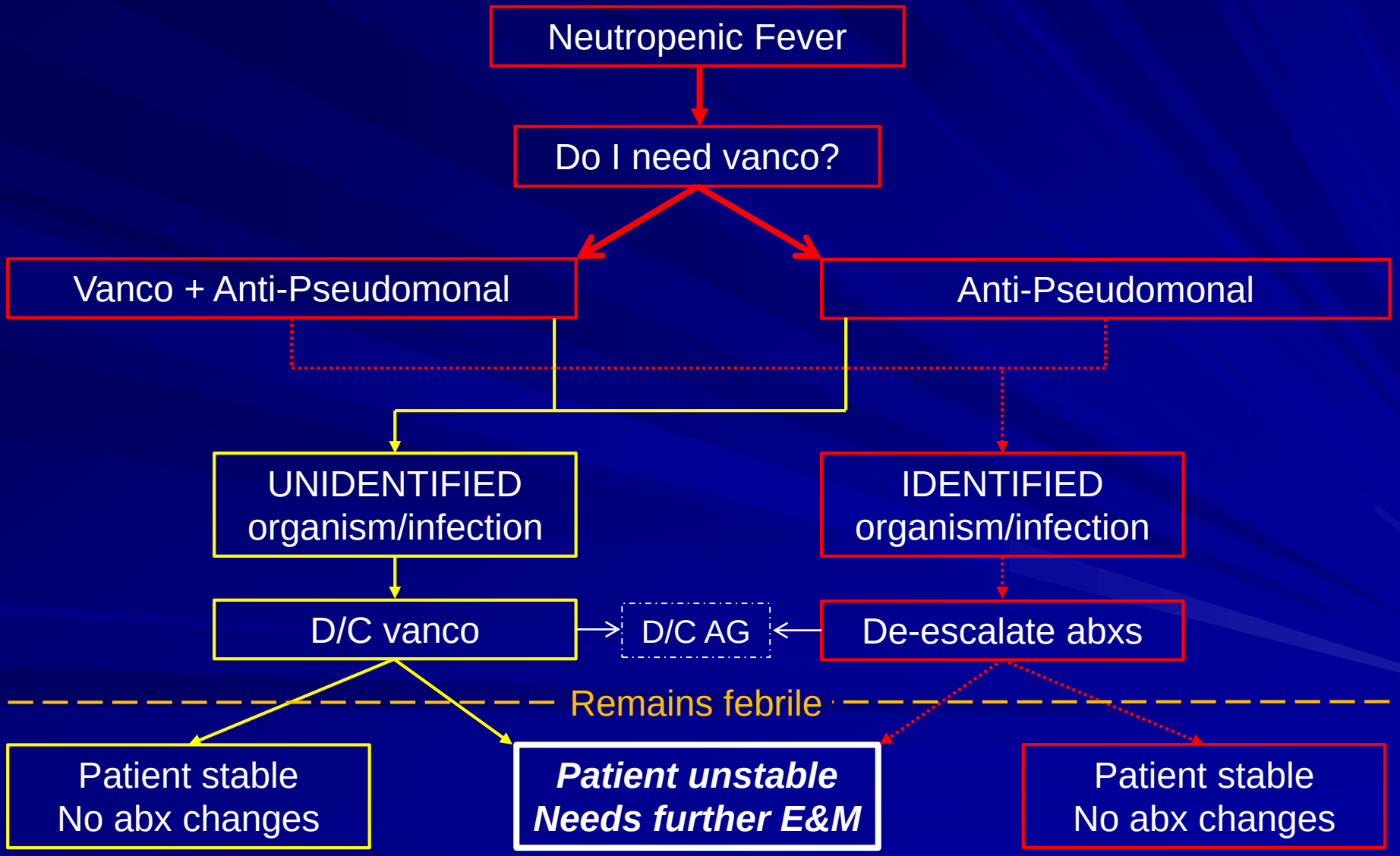
Antimicrobial Modification

17. Documented clinical and/or microbiological infections should be treated with antibiotics appropriate for the site and for the susceptibilities of any isolated organisms (A-I).

De-escalation of empiric antimicrobial therapy = avoid anti-pseudomonals

- Piperacillin/Tazobactam
- Cefepime
- Imipenem

Management Algorithm



Early Management Summary

- D/C vanco after 48 hours if no evidence of GP infection.
- No need to perform more BC after first 48-72 hours if patient clinically stable and no new symptoms.
- Can simplify regimen if organism isolated. No need to double cover Pseudomonas if sensitive to monotherapy.
- Median time to defervescence ~5 days.
- Treatment duration typically until ANC > 500.
- If clinical worsening:
  - Aggressive diagnostics
  - Modify antibiotics to cover for resistant organisms
  - Start anti-Candida therapy

65M AML admit induction chemo. PICC line placed. HD#12 neutropenia. HD#15 Tm 38.6^{0}C. Exam: OK. CXR neg. Patient started on cefepime. HD#17 still febrile 38.3^{0}C x 2d. D15 & D16 BCxs negative. HD#20 still febrile but clinically unchanged.

Next best step in management?

A Stop all antibiotics due to drug fever

B Switch to linezolid, imipenem, tobra

C Add on micafungin

D Add on liposomal amphotericin

E Obtain CT chest/abd/pelvis

Antifungal Therapy

28. Empirical antifungal therapy and investigation for invasive fungal infections should be considered for patients with persistent or recurrent fever after 4–7 days of antibiotics and whose overall duration of neutropenia is expected to be >7 days (A-I).

Most common fungal infections = Candida and Aspergillus

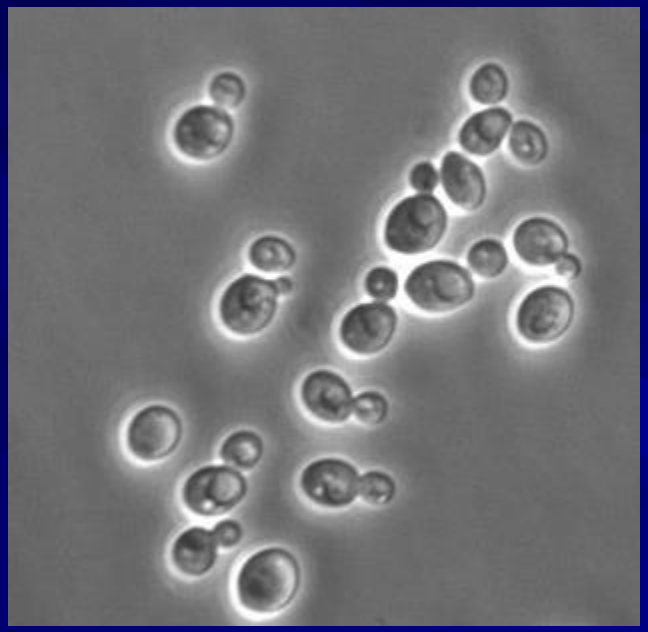
Candida:

- can occur “early” in the course of neutropenic fever
- primary manifestation = bloodstream infection

Aspergillus:

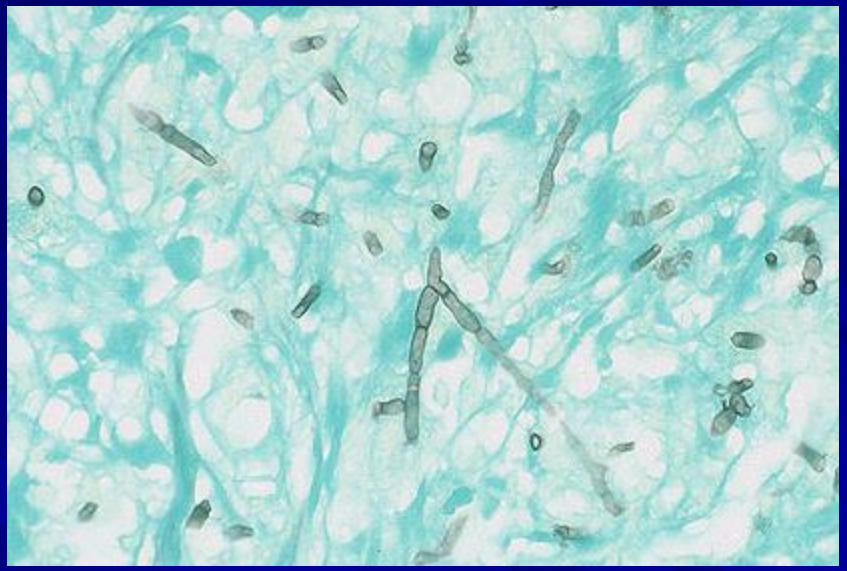
- severe neutropenia lasting at least 10-15 days
- primary manifestation = sinus and/or lung infection

Fungus 101



YEAST:

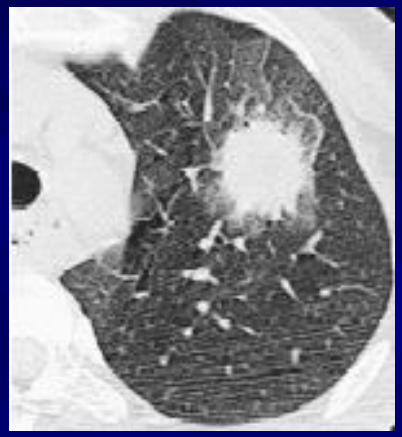
Candida, Cryptococcus



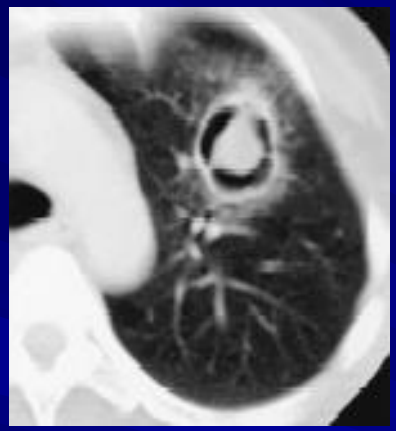
MOLD:

Aspergillus, Mucor

Invasive Mold



Halo sign



Air crescent sign

Aspergillus

Zygomyces

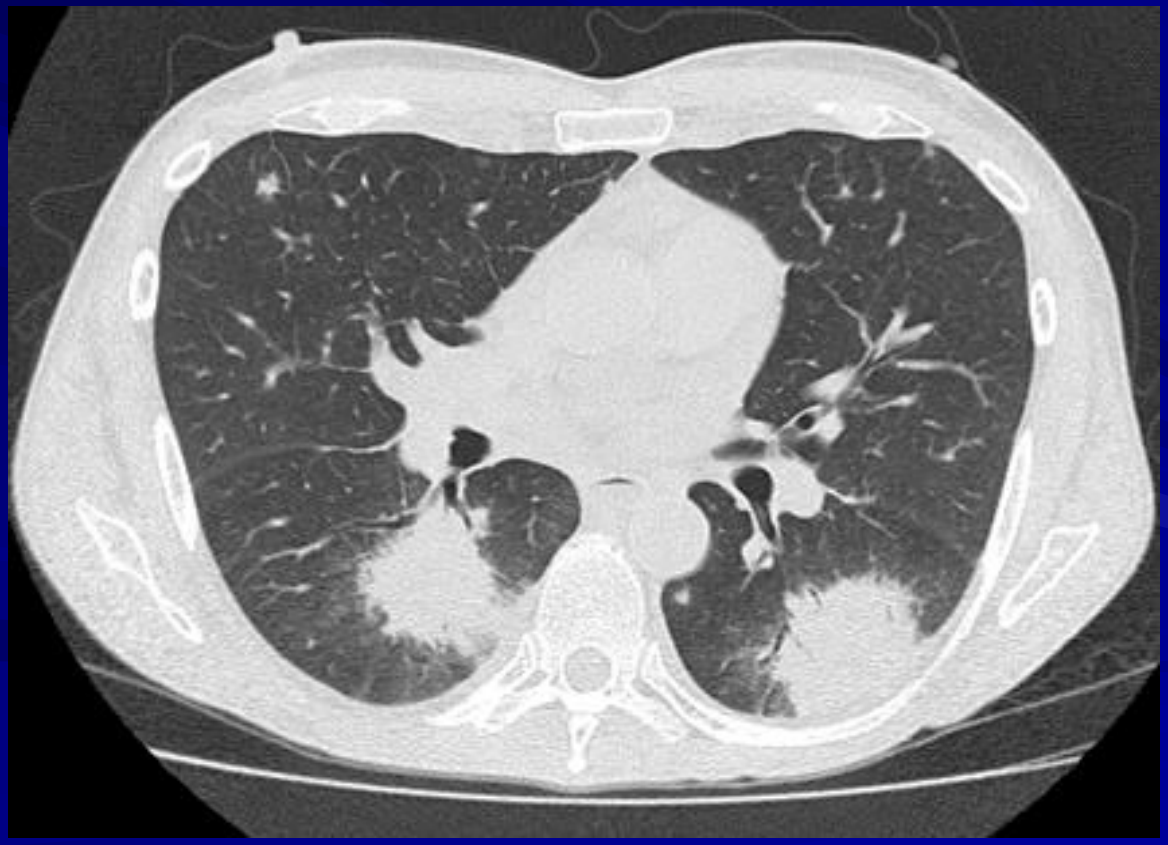
- Mucor
- Rhizopus
- Absidia

Fusarium

Halo sign, air crescent sign, cavitating nodule → Invasive mold

Abnormal CT chest → BAL with biopsy or IR guided biopsy

65M AML s/p induction chemo. Developed neutropenic fever HD#12 treated with cefepime and defervesced. Doing well but still neutropenic. HD#24 spikes new fever and CT chest performed. BAL with negative GS, fungal and AFB stains. Cultures pending.



65M AML admit induction chemo. PICC line placed. HD#7 neutropenia. HD#10 Tm 38.6^{0}C. Exam: OK. CXR neg. Defervesces on cefepime. HD#25 – Tm 39^{0}C, chest pain. Blood cxs obtained. CT chest with halo sign. What is the next best step in management?

A Start vanco

B Wait for culture results

C Add on micafungin

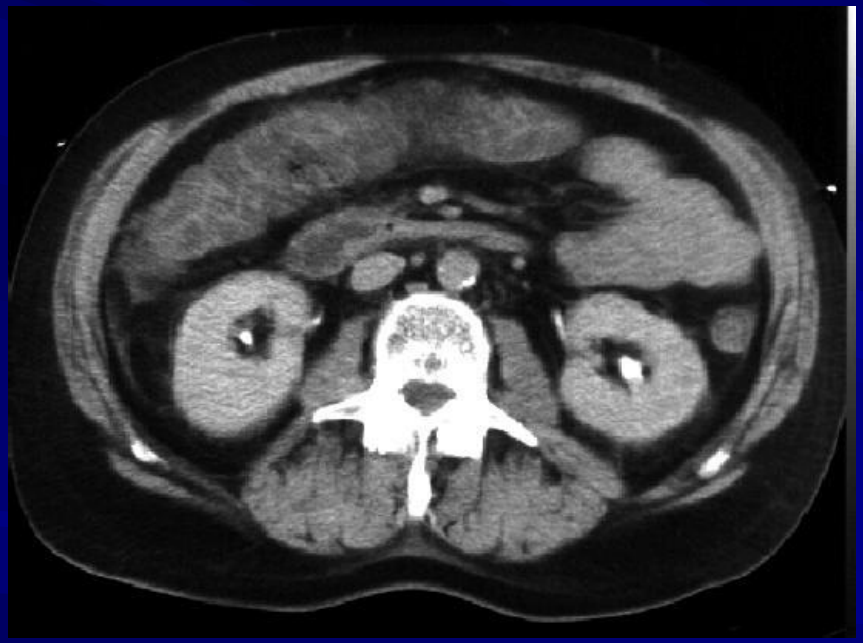
D Add on voriconazole

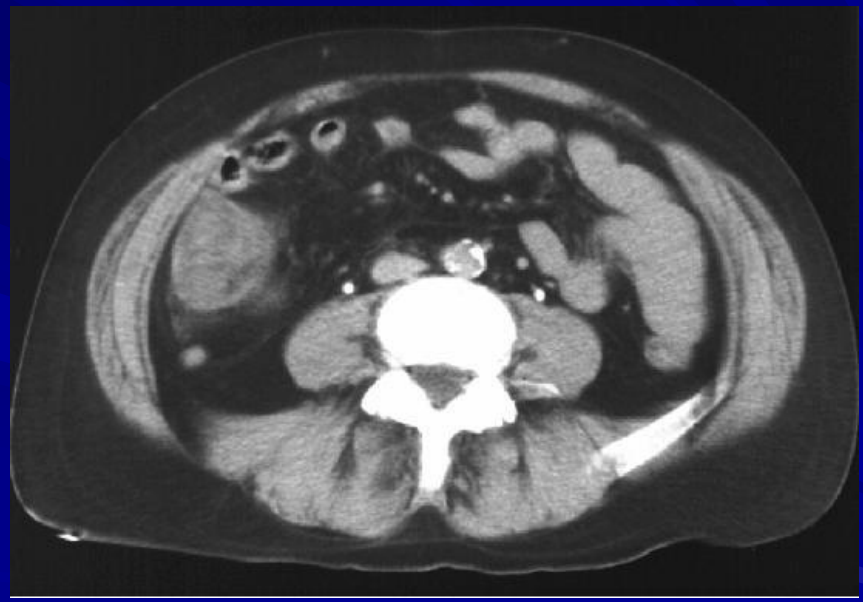
E Add on lipid amphotericin

Anti-Fungal Therapy

- Empiric:
  - Normal CT chest and/or sinus
  - Non-specific infiltrate on CT chest
  - No other evidence of invasive fungus
  - USE: Echinocandin or Amphotericin
- Presumed or Definite Invasive Aspergillus:
  - Classic CT chest findings (no previous Voriconazole)
  - Positive culture or biopsy with typical hyphae
  - Positive Galactomannan
  - USE: Voriconazole

65M AML s/p induction chemo. Develops neutropenic fever HD#12 with RLQ abdominal pain and diarrhea. Stool C.diff PCR negative. Blood cxs results pending, CT AP with findings below:





Colonic wall thickening from cecum to transverse colon

AML neutropenic fever HD#12. Patient with RLQ abdominal pain and diarrhea. Stool Cdiff PCR negative. CT Abd/Pelvis with colonic wall thickening. What is the next best step in management?

A Vanco (IV), cefepime, tobramycin

B Vanco (PO) and cefepime

C Cefepime and fluconazole

D Zosyn

E Vanco (IV & PO), Zosyn, Micafungin

Neutropenic Colitis

- Typhlitis
  - ANC < 500, usually AML
  - Abdominal pain
  - Diarrhea initially, ileus later
  - CT or US with bowel wall thickening
  - Rule-out C.diff
  - Need anaerobic coverage:
    - Zosyn, Imipenem, Cefepime + Metronidazole

Summary

- Neutropenic fever – definition and classification
  - High risk versus Low risk
  - Initial, Persistent, Recrudescent
- Microbiology
  - Bacterial translocation, CAI, HAI, opportunistic
- Clinical evaluation
  - Neutropenia = lack of inflammation
- Management
  - Initial NF – need Pseudomonas and Strep coverage
    - Vanco NOT routinely indicated
  - De-escalate empiric therapy after 48-72 hours
  - Persistent/Recrudescent NF – think fungal infection
  - Duration until ANC > 500