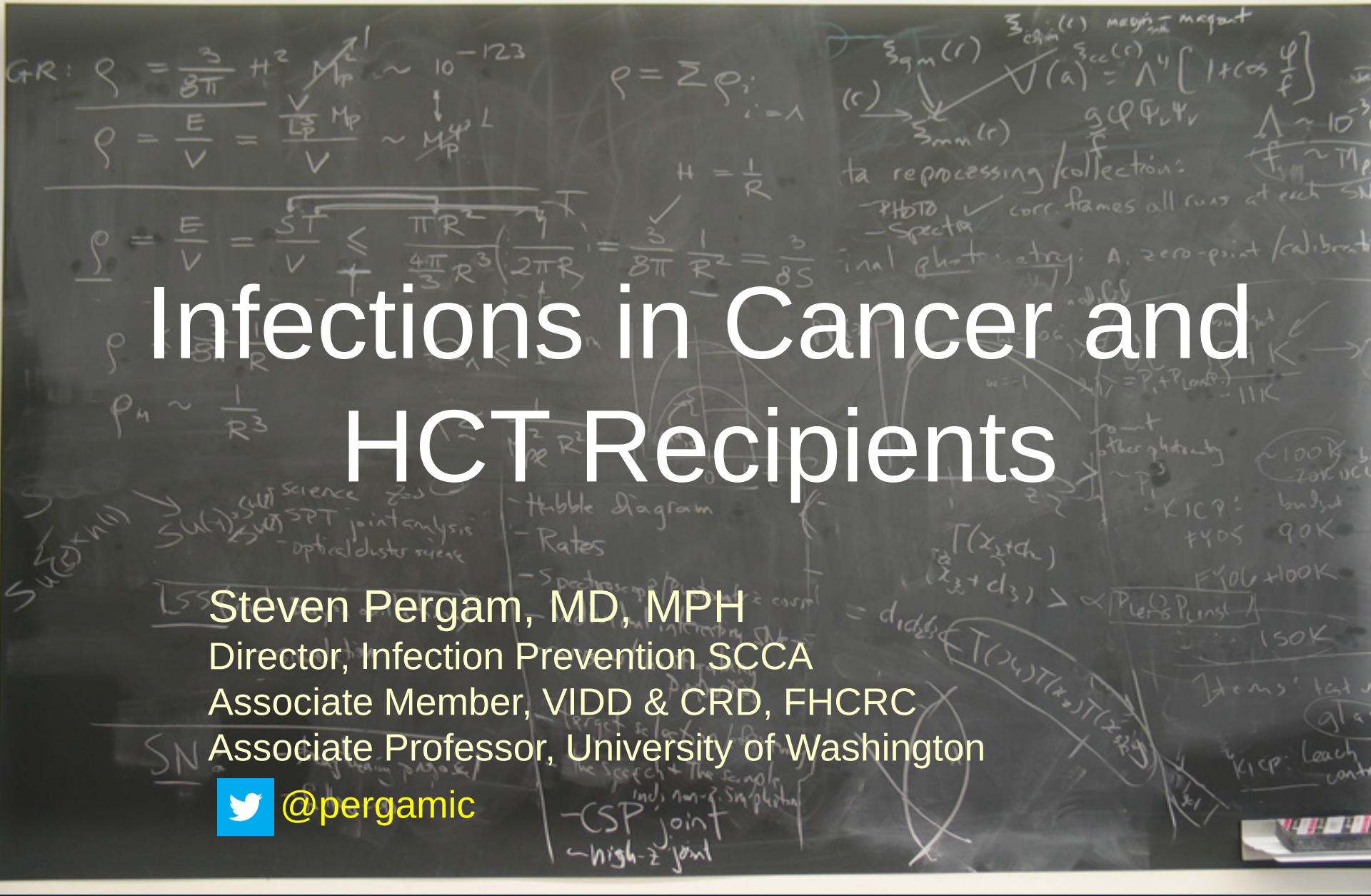


Infections in Cancer and HCT Recipients

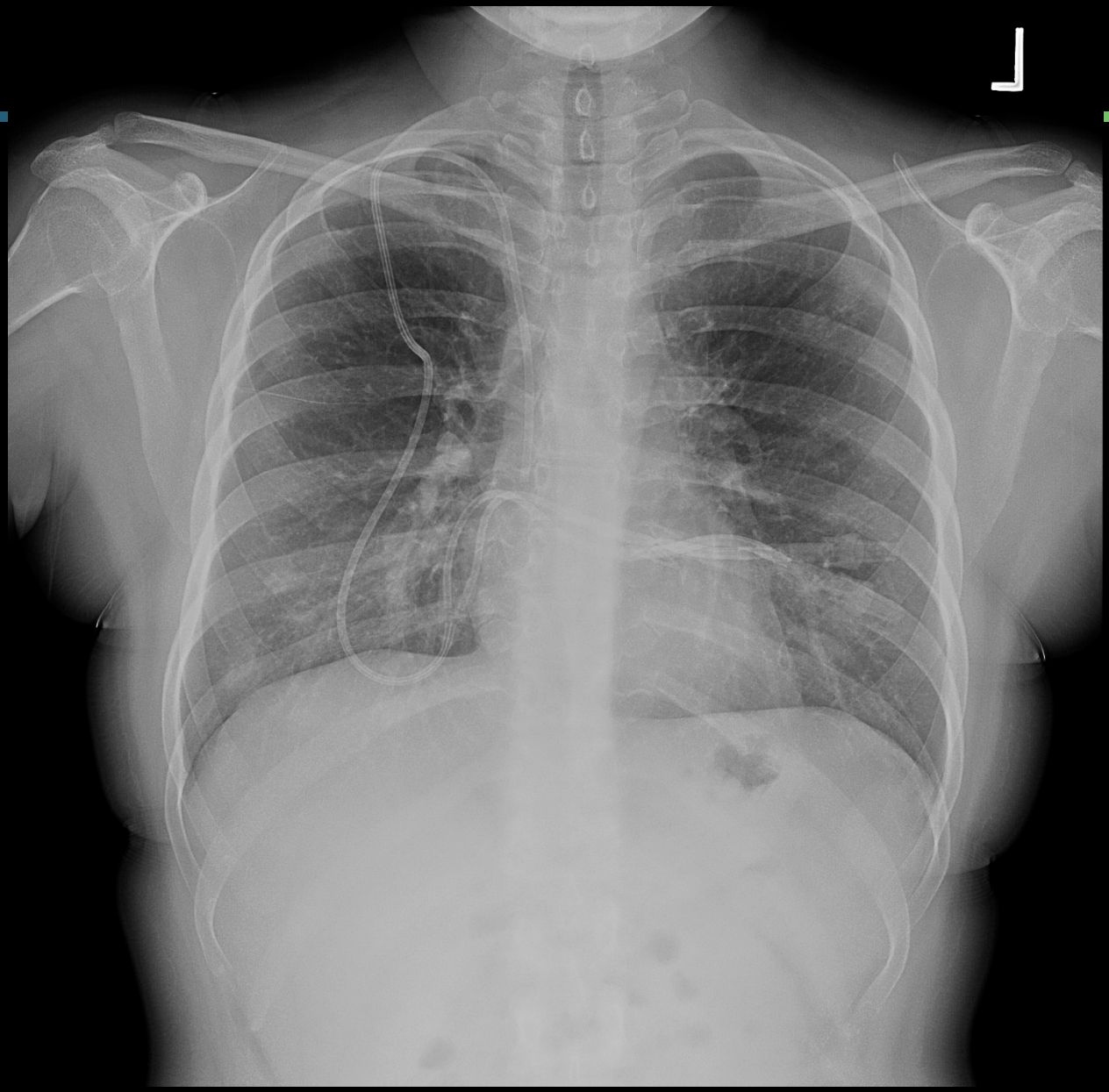
Steven Pergam, MD, MPH
Director, Infection Prevention SCCA
Associate Member, VIDD & CRD, FHCRC
Associate Professor, University of Washington
@pergamic

Case Presentation

- 27 y/o female with acute myelogenous leukemia in 1st remission
- Myeloablative conditioning with Cytoxan/TBI
- Received a double cord blood transplant
- Posttransplant period complicated by *Serratia* bacteremia, gut GVHD requiring 1 mg/kg of steroids, and low level CMV reactivation

Case Presentation

- Day +24 developed abdominal pain after discharge, seen in clinic and CT of abdomen negative
- Planned GI appointment for endoscopy
- Following day complained of fevers in clinic so admitted
- On arrival to hospital tachypnea, and hypoxic to 88% on RA



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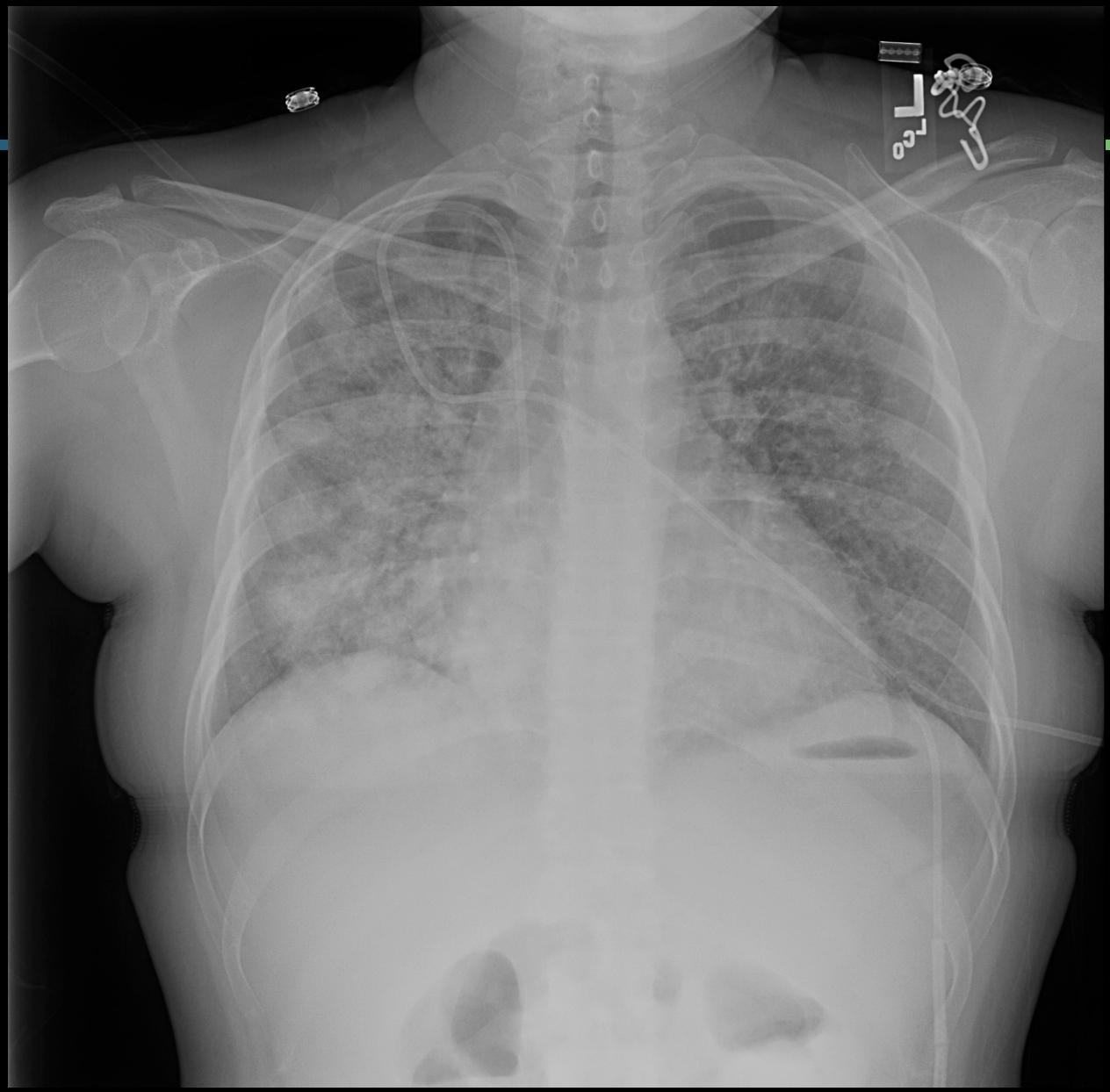
Case Presentation

- Empiric Ceftazidime and Vancomycin started
- Continued to complain of abdominal pain and hypoxia worsened
- Moved to ICU and non-rebreather mask
- Ceftazidime changed to meropenem and ganciclovir started
- Repeat chest x-ray



Immunosuppression Pre and Post

- Radiation
- Cytotoxic chemotherapy
- Steroids
- Calcineurin inhibitors
- mTOR inhibitors
- MMF
- Antibody therapy
  - Alemtuzumab / ATG
  - Monclonal antibodies
- TNF inhibitors
- Proteasome inhibitors
- Immunotherapy

Additional Risks for Infections

- **Neutropenia (pre & post)**
- Lymphopenia
- Delayed T-cell recovery
- **Mucosal barrier injury**
- Integument breakdown
- Blood transfusions
- **Prior antibiotic use**
- **Gastric acid suppression**
- Prolonged hospitalization
- **Central lines**
- TPN/PPN use
- Colonization with MDROs
- Renal/Liver dysfunction
- Splenectomy
- Age/Obesity
- Iron overload

Taking their meds?

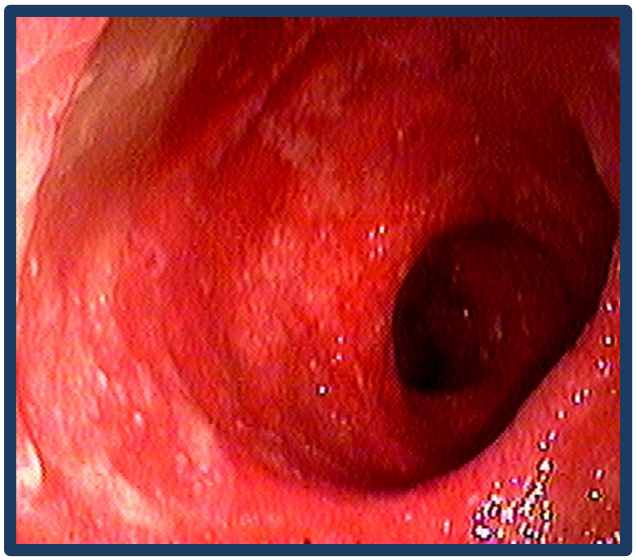
Are you sure your patient is taking their:

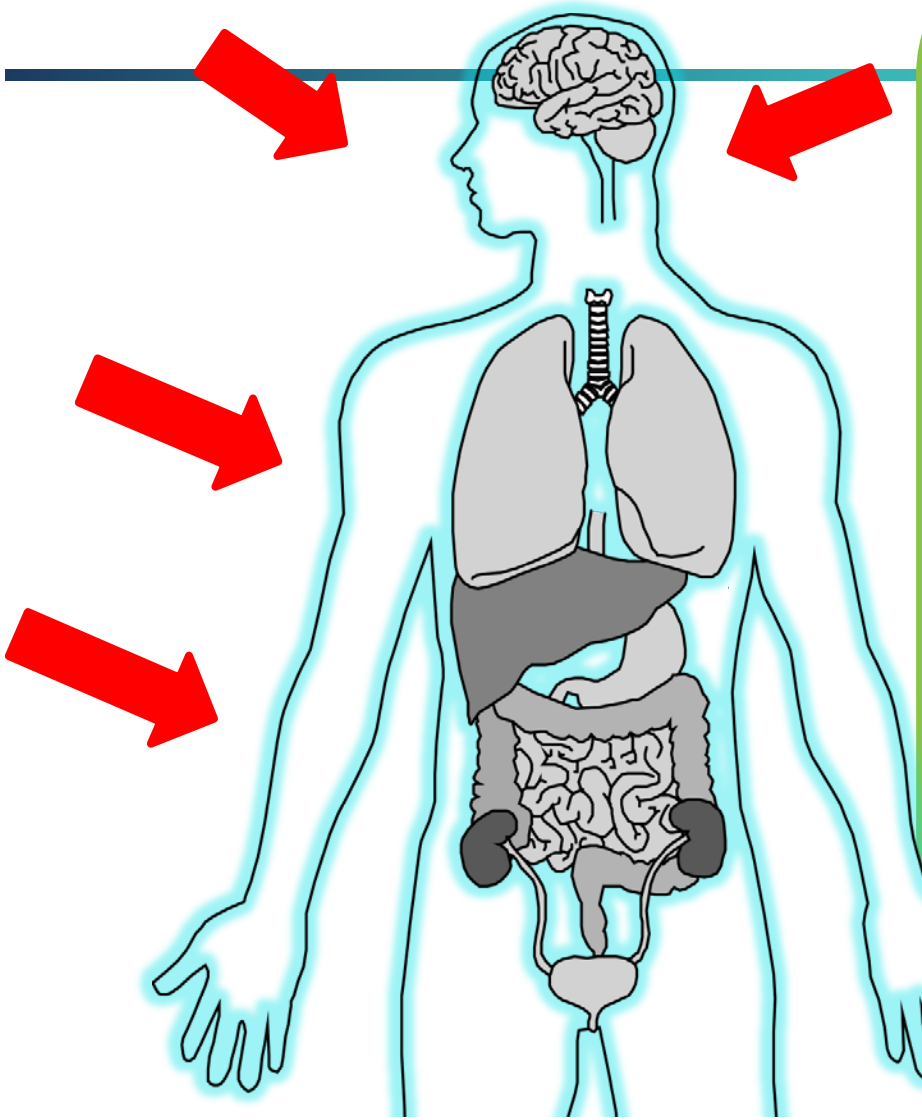
- Bactrim?
- Acyclovir?
- Fluconazole?
- Posaconazole?

From the marrowmovement.com

Complications Increase Risk

- Engraftment syndrome
- Graft-versus-host-disease
  - Need for steroids/ATG
  - Acute vs. Chronic
- Delayed engraftment/graft failure
- Rituxan/ATG
- Mucositis
- Drug side effects





External Microbial Agents

Viruses
Influenza
RSV
Paraflu
Adenovirus
Norovirus
Enteroviruses
Legionella

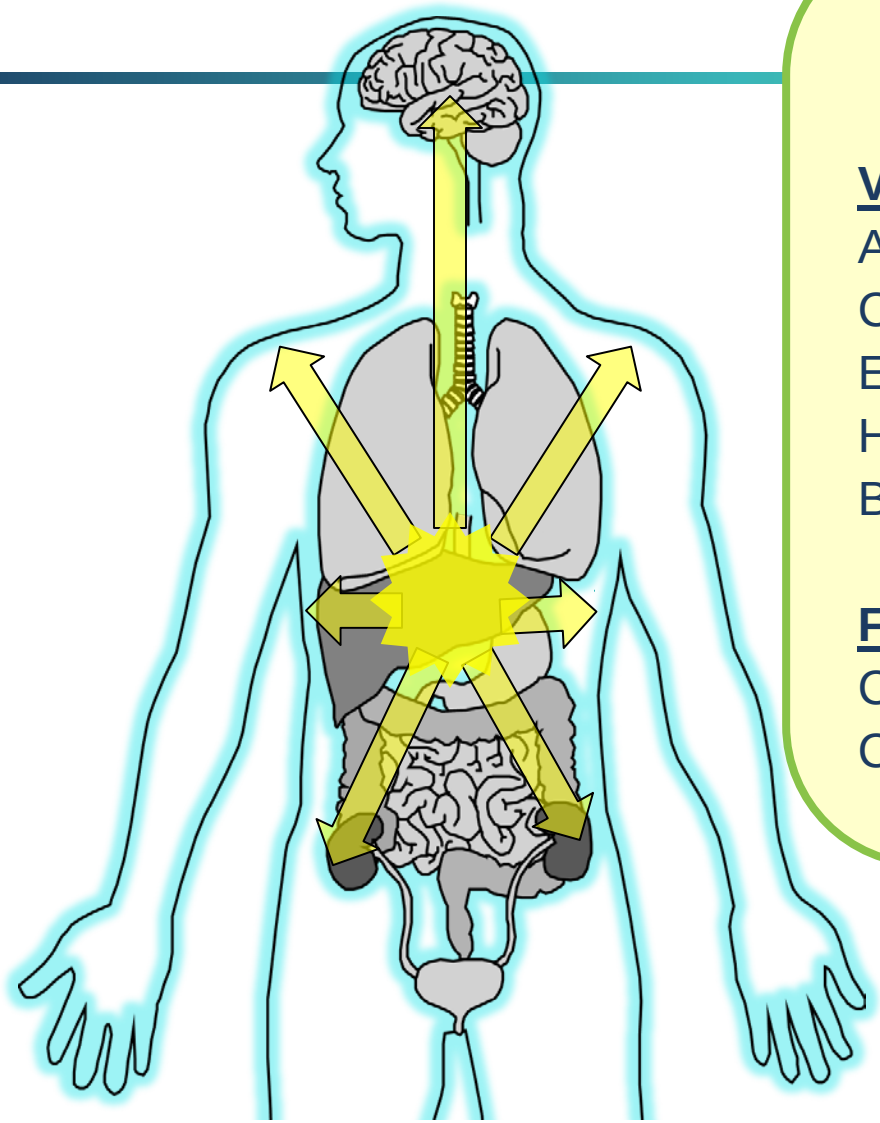
Bacteria
VRE
MRSA
Resistant GNR
Nocardia
C Difficile

Parasites
Toxoplasma

Fungi
Aspergillus
Murcorales
Cryptococcus

FRED HUTCH

Image by Kyoko Kurosawa



Internal Microbial Agents

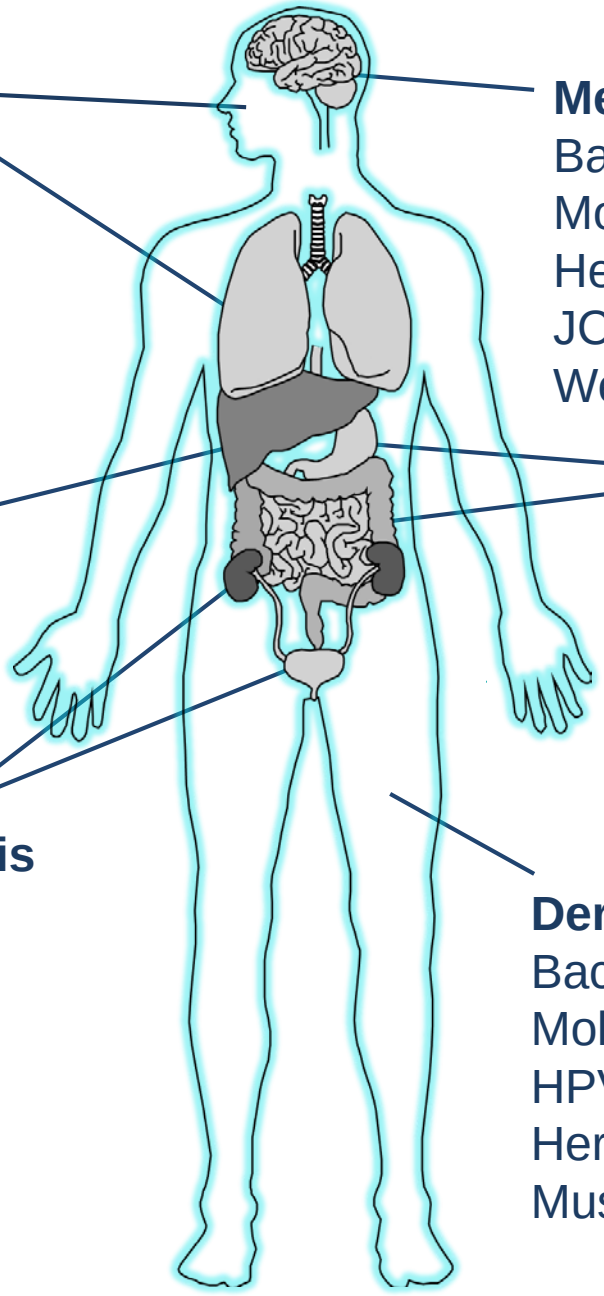
Viruses
- Adenovirus
- CMV
- EBV
- HHV-6
- BK/JC Virus

Bacteria
- Enteric GNRs
- Skin flora
- MTB
- Strep viridans/ oral flora

Fungi
- Candida
- Cocci / Histo

Parasites
- Strongylodiasis
- T cruzi
- Toxoplasma

Image by Kyoko Kurosawa



Sinopulmonary
Bacterial
Mold/Yeast
Respiratory viruses
Adenovirus
Herpesviruses (CMV)
Toxoplasmosis
PCP

Meningitis/Encephalitis
Bacteria
Mold/Yeast
Herpesviruses
JC virus
West Nile virus

Gastritis/Colitis
Bacteria
Mold/Yeast
Adenovirus
Norovirus
Herpesviruses
Parasite/Protozoa

Hepatitis
Adenovirus
Herpesviruses
Mold/Yeast

Cystitis/Nephritis
Bacterial
Mold/Yeast
Adenovirus
BK virus

Dermatologic
Bacterial
Mold/Yeast
HPV
Herpesviruses (VZV)
Musculosum contagiosum

Modified from Lennette's Laboratory Diagnosis of Viral Infections, 4th Addition

Image by Kyoko Kurosawa

Consider common infections

- Bacteria
- Fungi
- Viral infections
- **Multiple infections**
- ***Infection Mimics***

Consider timing

- Timing of neutropenia?
- How long neutropenic?
- Early during inpatient management?
- After returning to the community?
- After completing prophylaxis?
- During prophylaxis?
- Recent chemotherapy/What type?
- Steroid use?

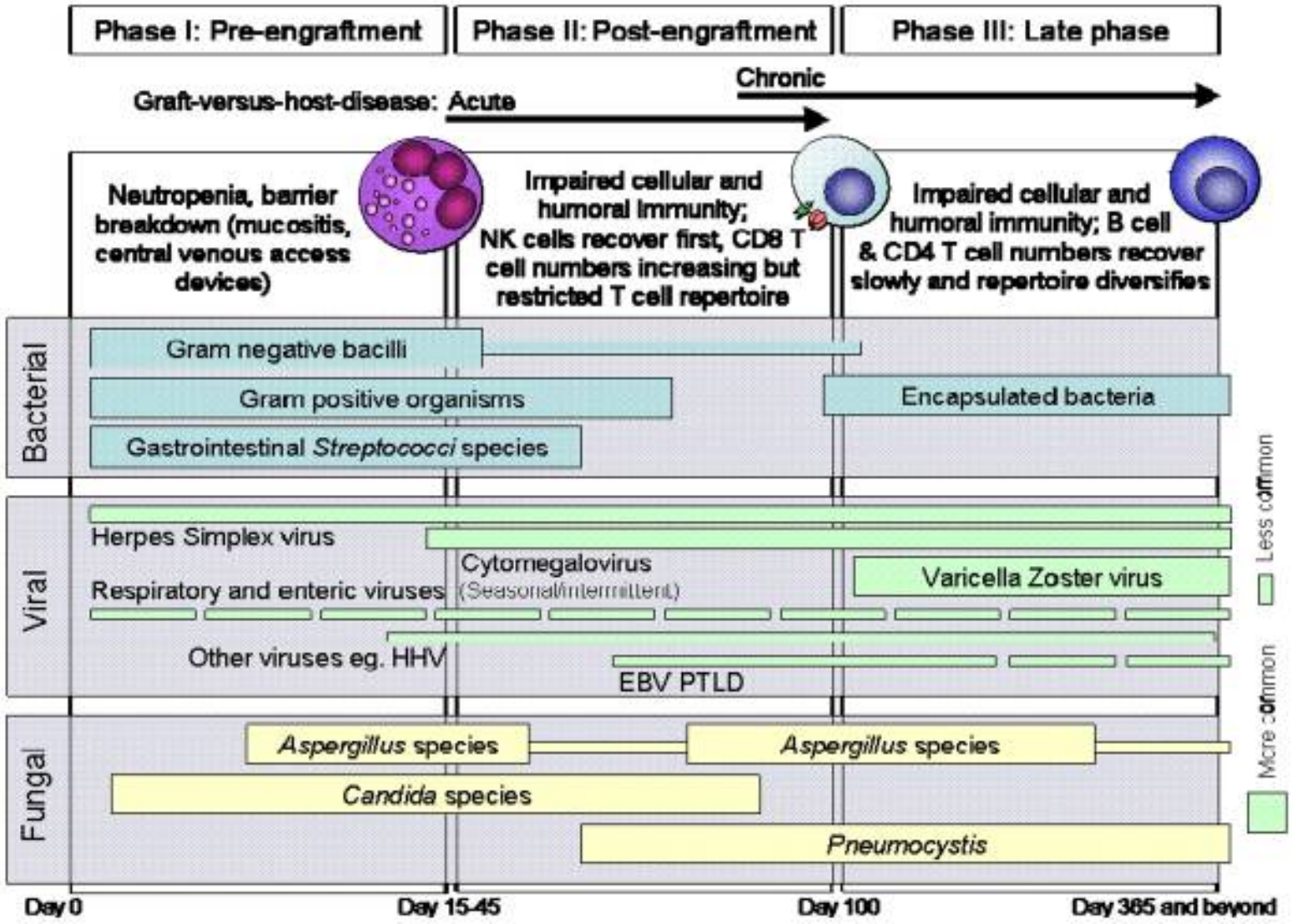
IC Hosts and Infections

- Consistent timeline for major pathogens
- Common bacteria, viruses and fungi are common
- Atypical presentations: mild presentations of major pathogens/rapidly progressive minor pathogens, uncommon symptoms
- Minor illnesses = Significant morbidity & mortality
- Unique infections / Rare presentations
- **Pay attention to symptoms**

Palatal lesion?

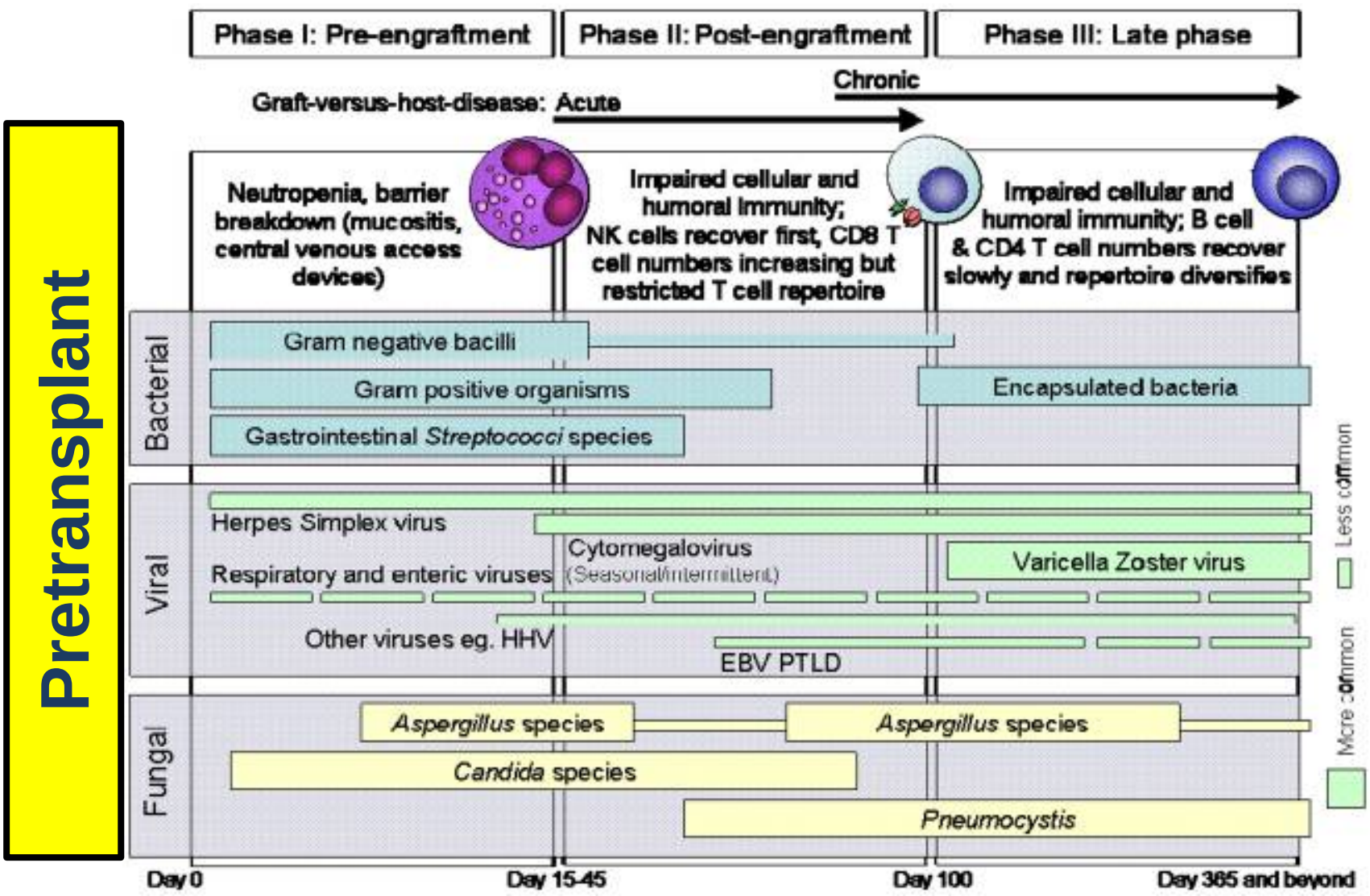
Palatal lesion? Mold

Hematopoietic Cell Tx Infection "Timeline"



Tomblyn BBMT 2011

Hematopoietic Cell Tx Infection "Timeline"



Tomblyn BBMT 2011

Prevention /Prophylaxis

CMV – Acyclovir / Ganciclovir / Valganciclovir

HSV – Acyclovir

Fungal – Fluconazole / Posaconazole / Voriconazole

PCP – Bactrim / Dapsone / Atavaquone

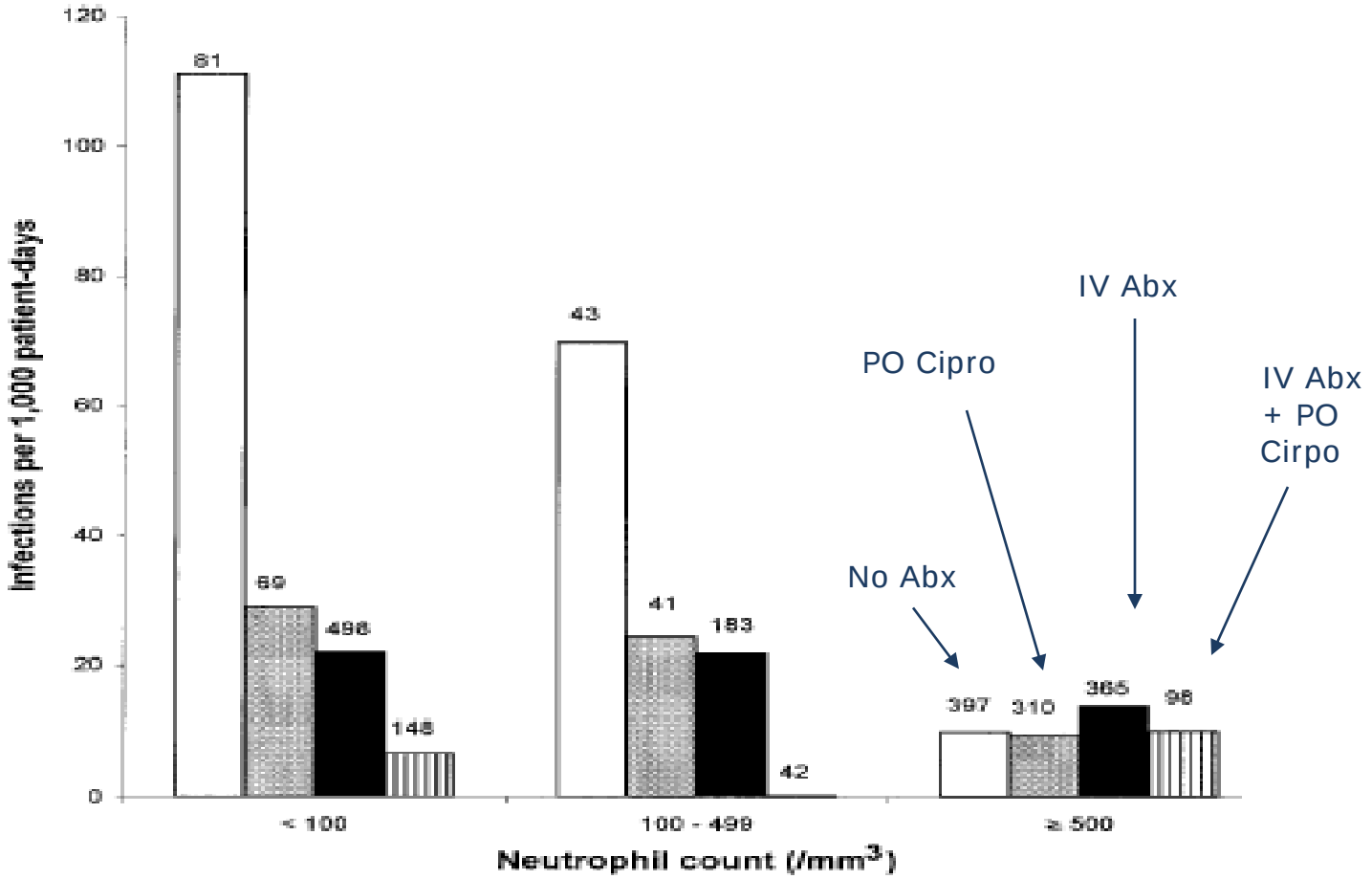
Toxoplasmosis - Bactrim

Encapsulated bacteria – Bactrim / Pen VK

Neutropenia – Flouroquinolones

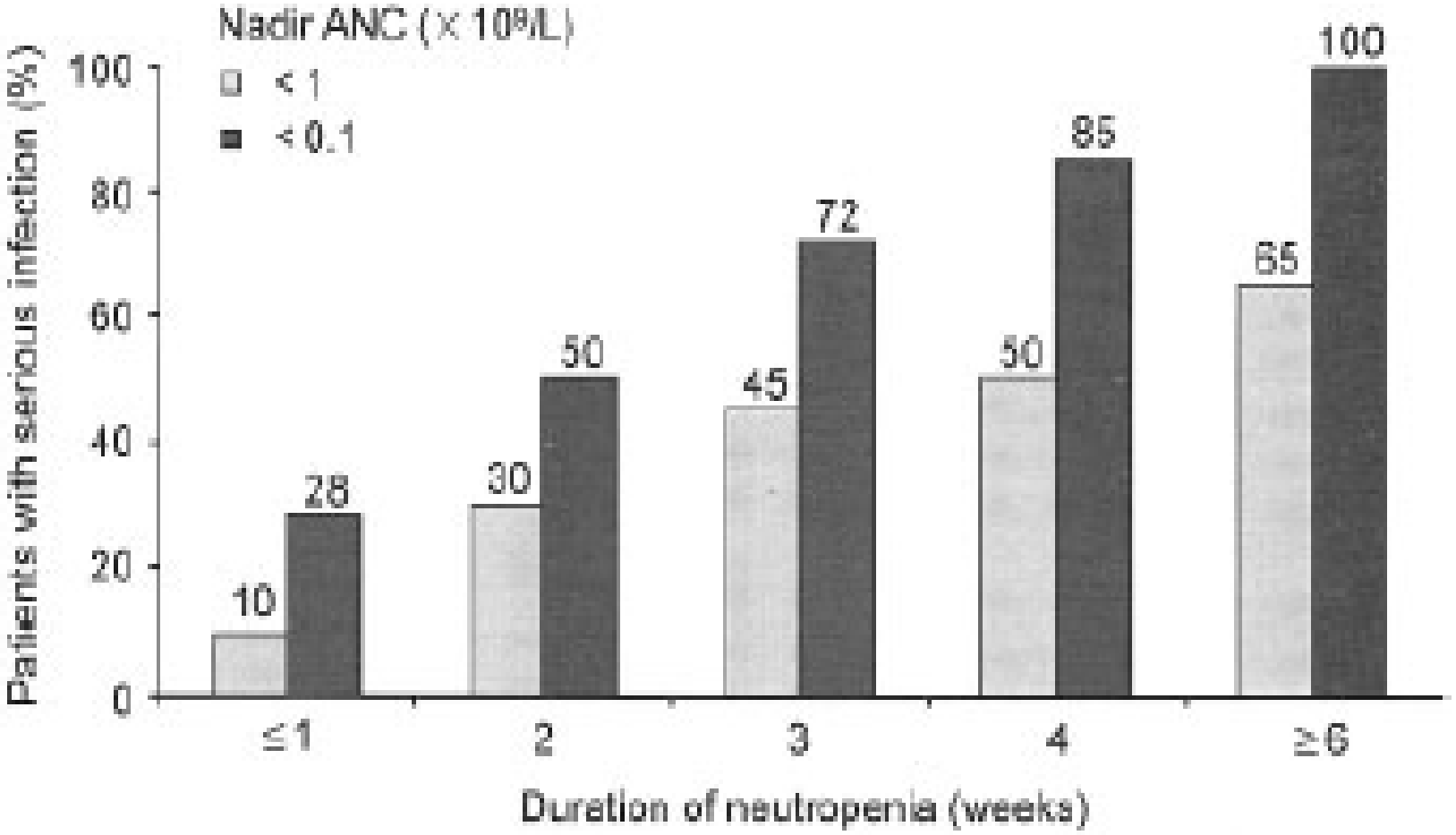
Hepatitis B – Lamivudine / Entecavir

Risk Factors for Infection: Why 500?



Engels EA (1999). *Clin Infect Dis*

Risk Factors for Infection: Duration



Viscoli C (2005), *Clin Infect Dis*

Primary prophylaxis for neutropenia

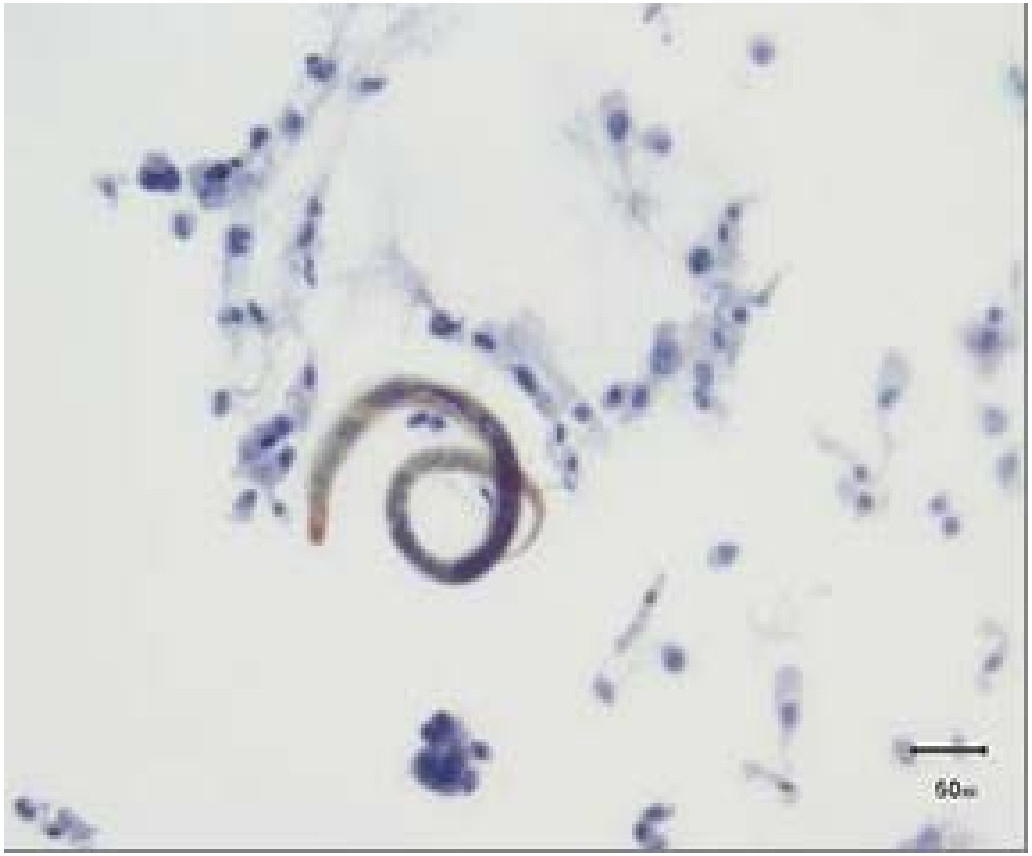
- Levofloxacin
- TMP/S
- Amox/Clav
- IV Ceftazidime
- Nothing

Emerging data suggesting potential benefits of no prophylaxis (microbiome/resistance)– but currently not policy here yet

Case

- 46 y/o Laotian man undergoing chemotherapy for ALL
- ANC 0
- Fever to 101 and shaking chills
- Started on Cefepime, hypotension moved to ICU
- Blood cultures grow *E. coli, Enterobacter cloacae,* and *Citrobacter furundii*
- Diffuse pulmonary infiltrates and acute respiratory failure, undergoes a BAL after intubation
- Diagnosis is…..

BAL results…..



Prevention /Prophylaxis

CMV – Acyclovir / Ganciclovir / Valganciclovir

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Neutropenia – Flouroquinolones

Hepatitis B – Lamivudine / Entecavir

Strongylodiasis – Ivermectin (Travel history Key!)

Pre-Engraftment (0 - ~Day +15)

- 35 y/o s/p Bu/Cy day 5
- Severe mucositis & neutropenia
- On Levofloxacin prophylaxis
- Develops fever to 101.5 and chills
- Cultures pending
- What are common cause of early fever?

Pre-Engraftment (0 - ~Day +15)

- 35 y/o s/p Bu/Cy day 5
- Severe mucositis & neutropenia
- On Levofloxacin prophylaxis
- Develops fever to 101.5 and chills
- Cultures pending
- What are common cause of early fever?

Bacteria – GPC > GNR, C diff

Fungal infections – Yeast (candida) >> Mold

Respiratory viruses

Pre-Engraftment (0 - ~Day +15)

- 35 y/o s/p Bu/Cy day 5
- Severe mucositis & neutropenia
- On Levofloxacin prophylaxis
- Develops fever to 101.5 and chills
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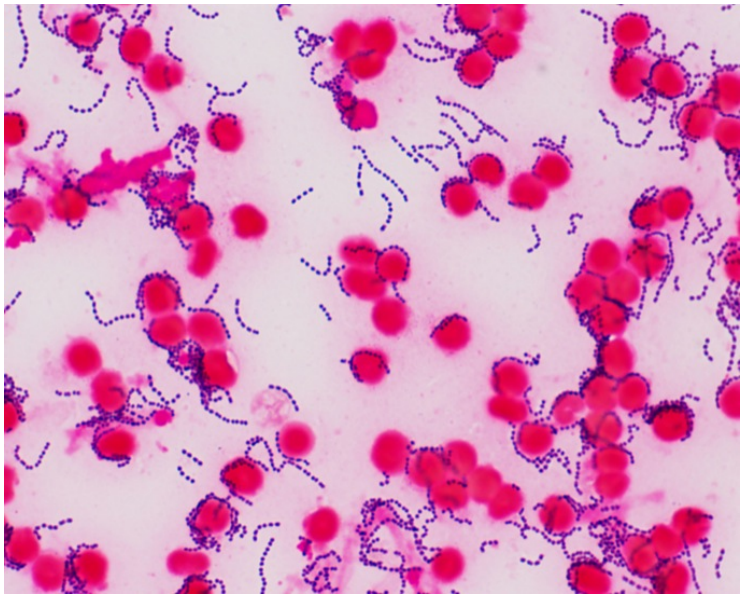


Viridans streptococcal bacteremia = common early post-transplant phase and more often seen in patients with severe mucositis (often resistant to FQs)

Case

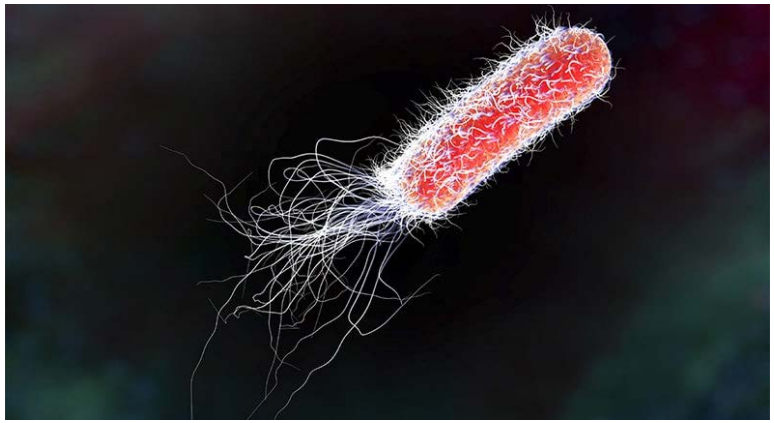
- 57 y/o male s/p MURD HCT
- Count recovery on day +22
- Now Day +57
- Course complicated by gut GVHD requiring first 1 mg/kg, and then 2 mg/kg prednisone
- Diarrhea improving, but remains on 60 mg day of prednisone on slow taper
- Over 48 hours develops hypotension and hypoxia (moved to ICU), now growing GNR in blood

Primary empiric regimens?

- IV cefepime
- IV vancomycin (if bad mucositis, or presumptive line infection)
- Meropenem in patients with:
  - known history of MDR-GNR pathogens
  - in patients with presenting with sepsis like symptoms
  - apparent GI/abdominal infection

Most common GNR in HCT patients?

- ***E coli (#1)***
- *Stenotrophomonas maltophilia*
- *Pseudomonas aeruginosa*
- *Enterobacter cloacae*
- *Klebsiella pneumonia*



Which is intrinsically resistant to Meropenem?

- *E coli*
- *Stenotrophomonas maltophilia*
- *Pseudomonas aeruginosa*
- *Enterobacter cloacae*
- *Klebsiella pneumonia*

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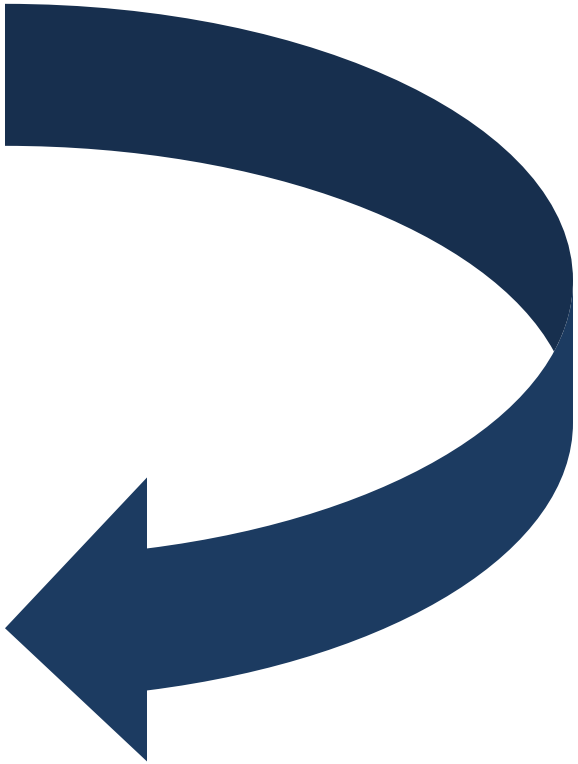


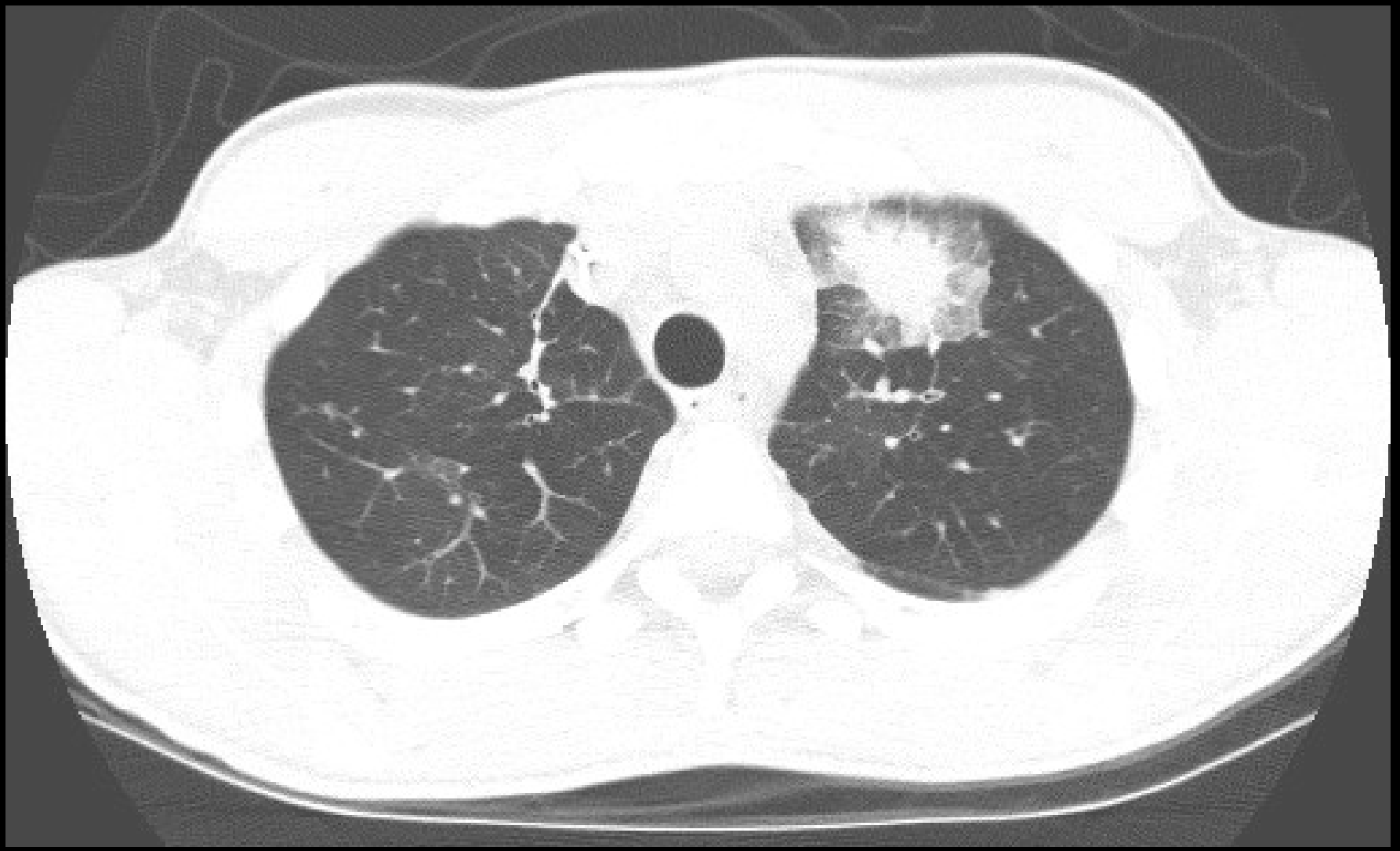
Treatment of choice = Bactrim

Higher risk for GNRs?

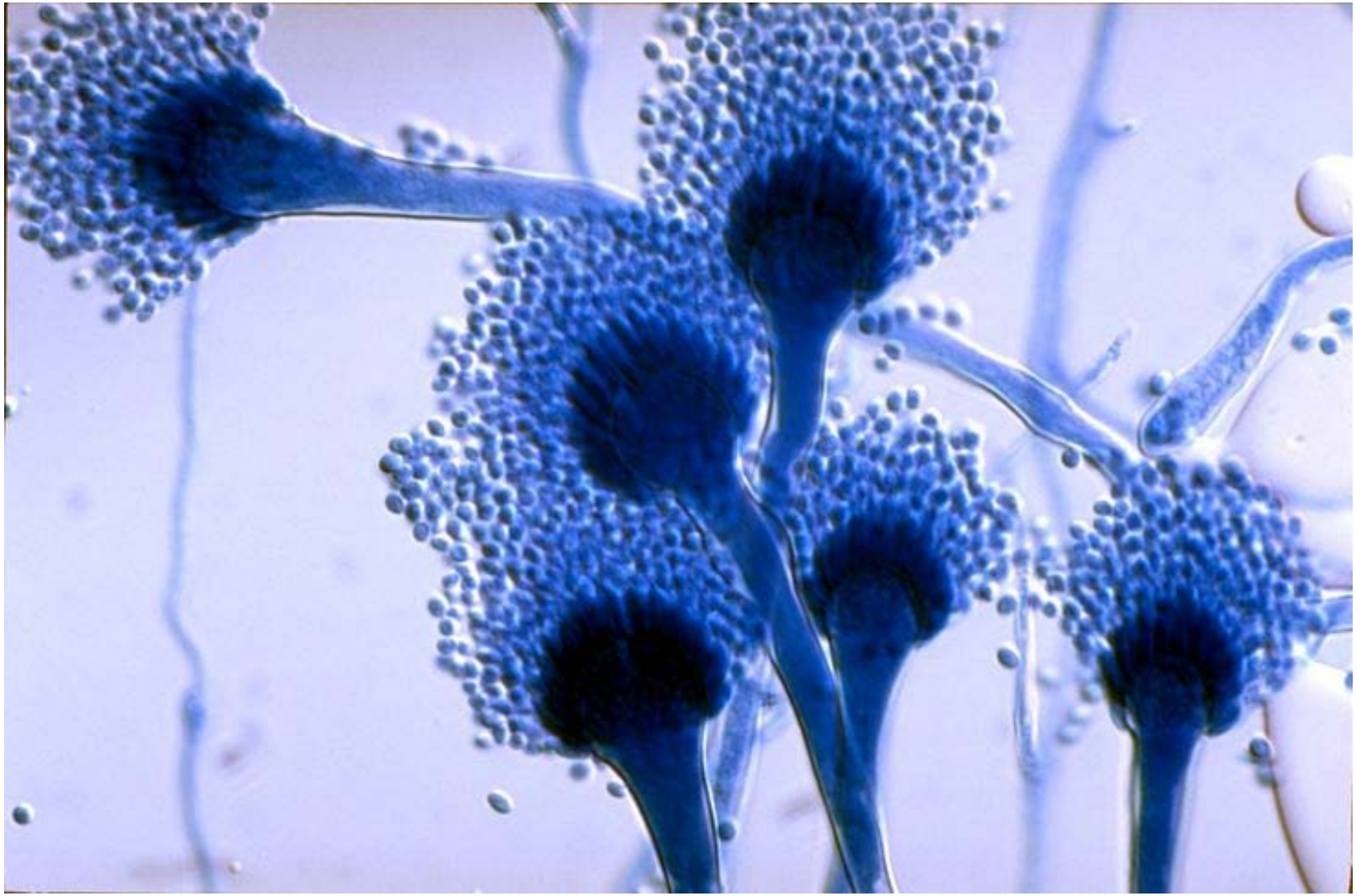
- Gut GVHD
- High-dose steroids
- Severe mucositis
- Neutropenia
- Prior colonization with MDR GNR
- Prolonged antibiotics (↑ resistance)

Case

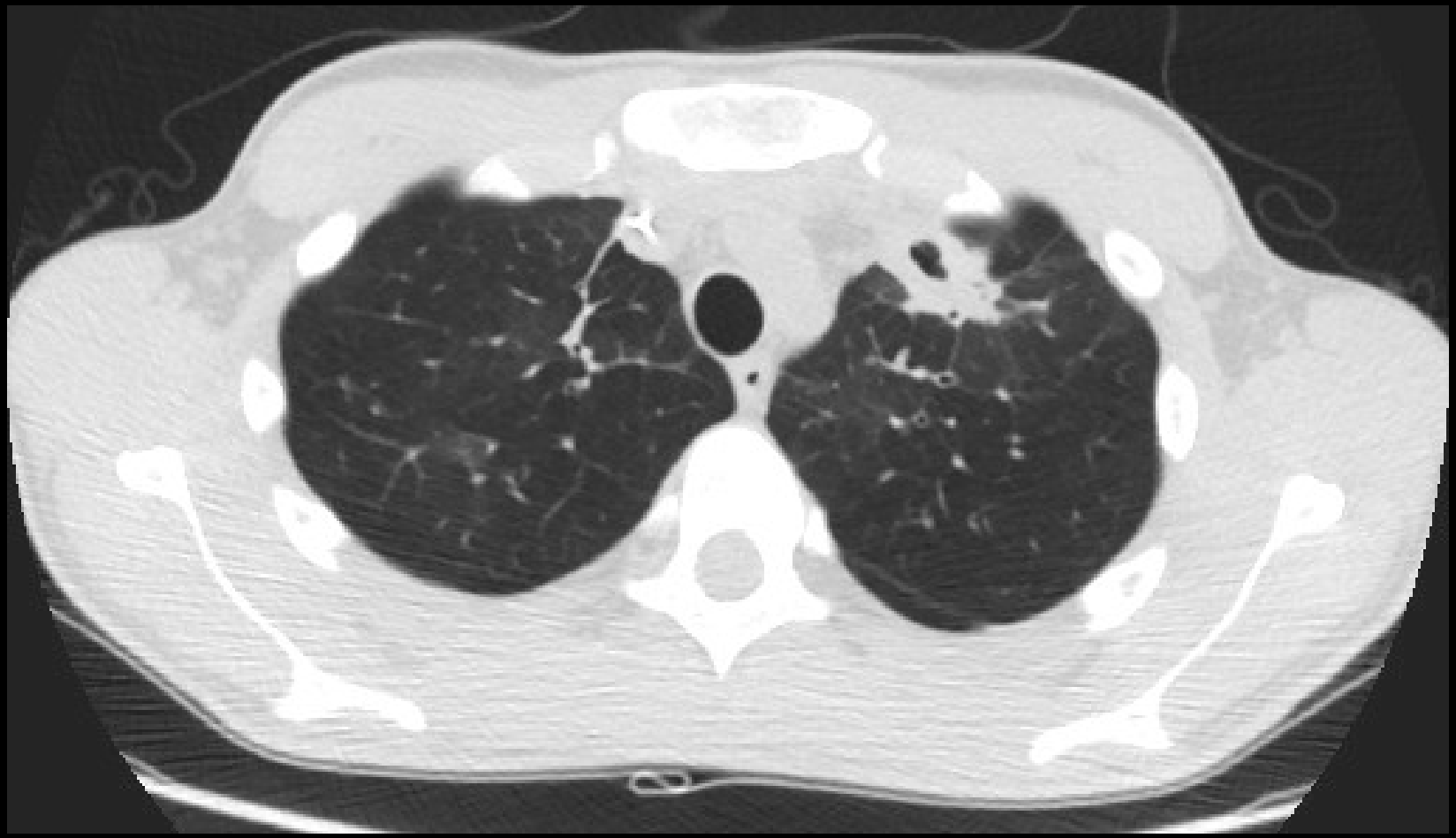
- 28 y/o male with AML, s/p G-CLAM
- Day +22 of neutropenia
- Admitted with neutropenic fever and work-up negative
- Treated with IV Cefepime
- Develops dry cough
- Abnormal chest x-ray – so gets CT scan

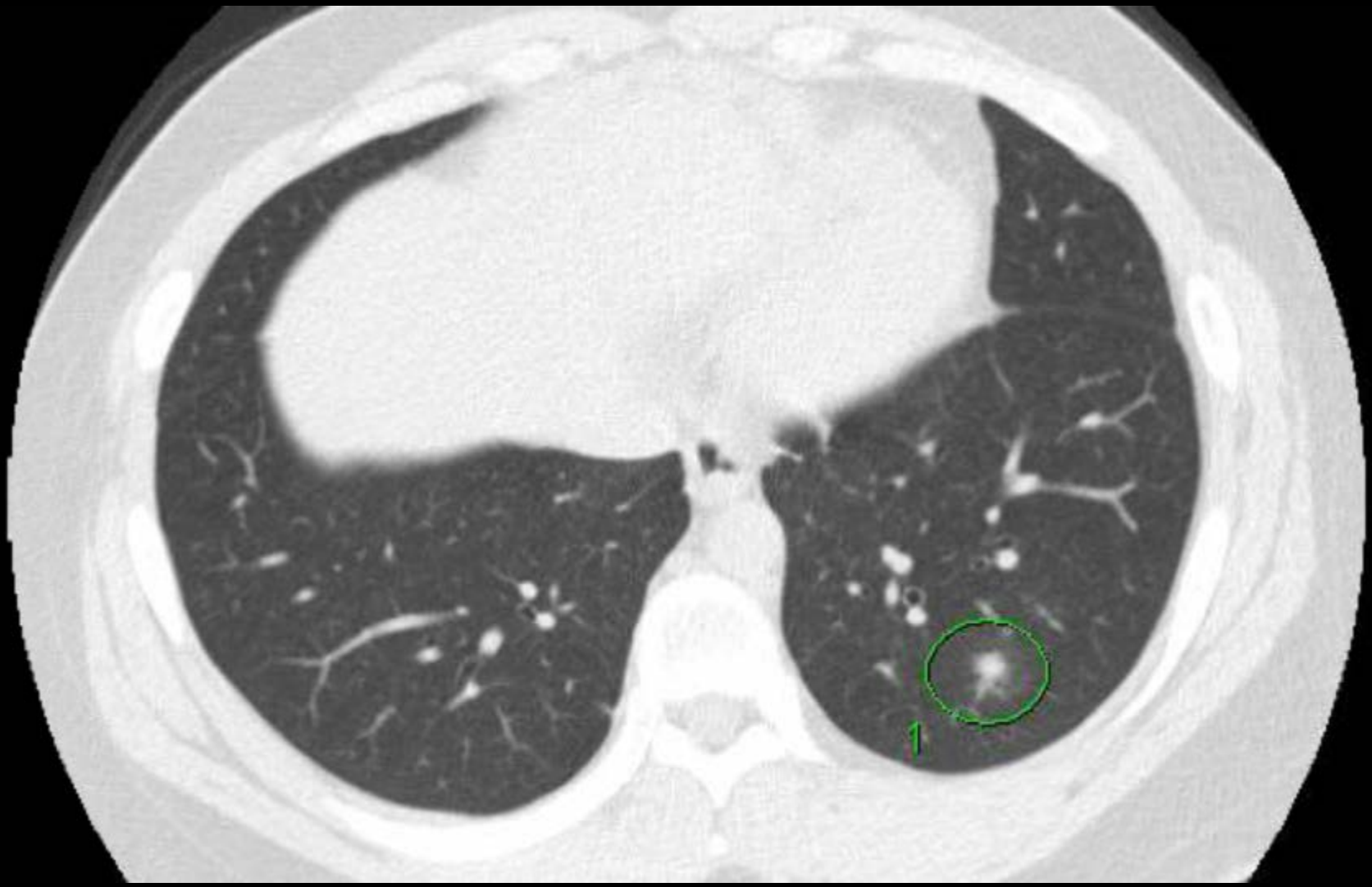


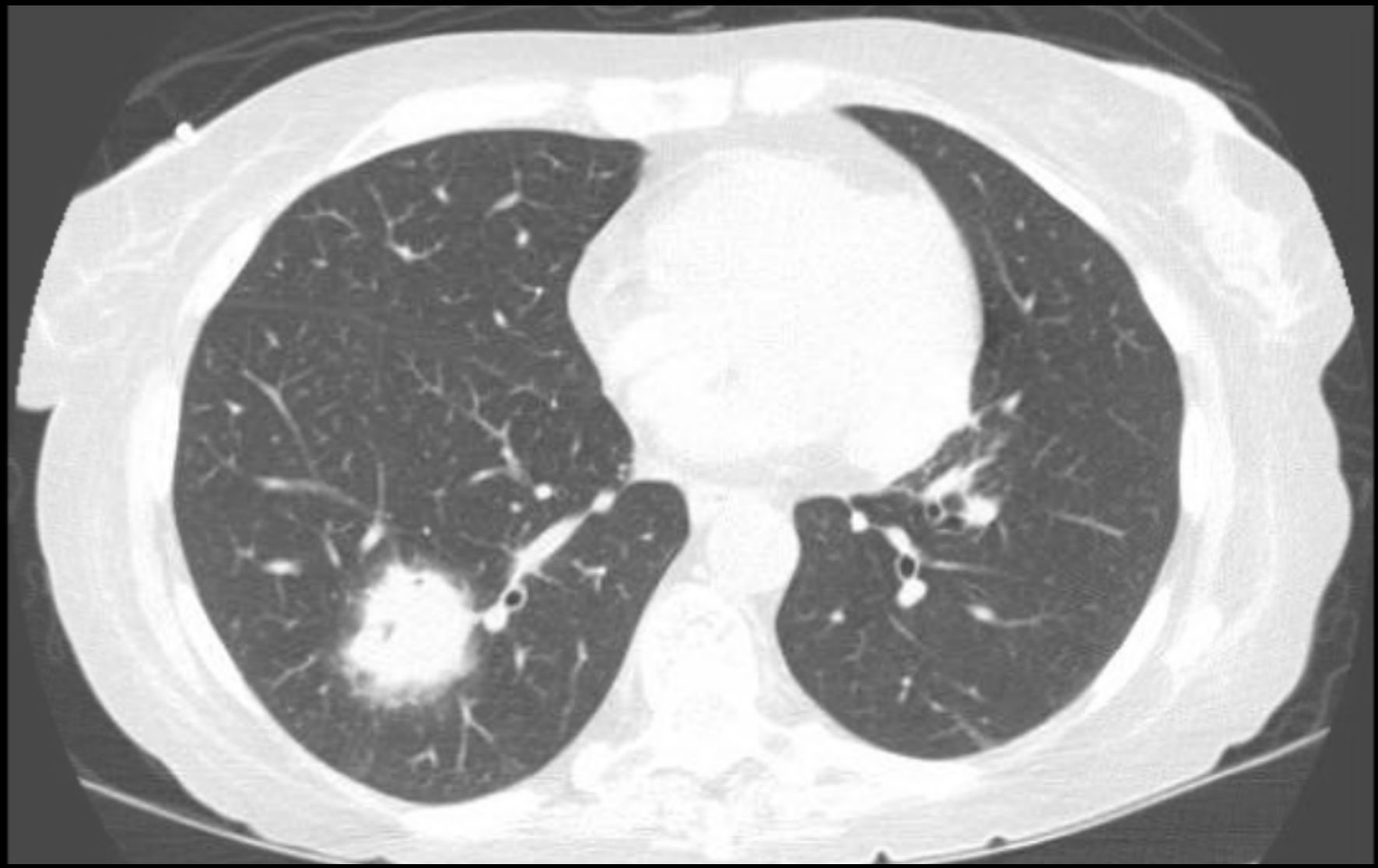
Aspergillus pneumonia

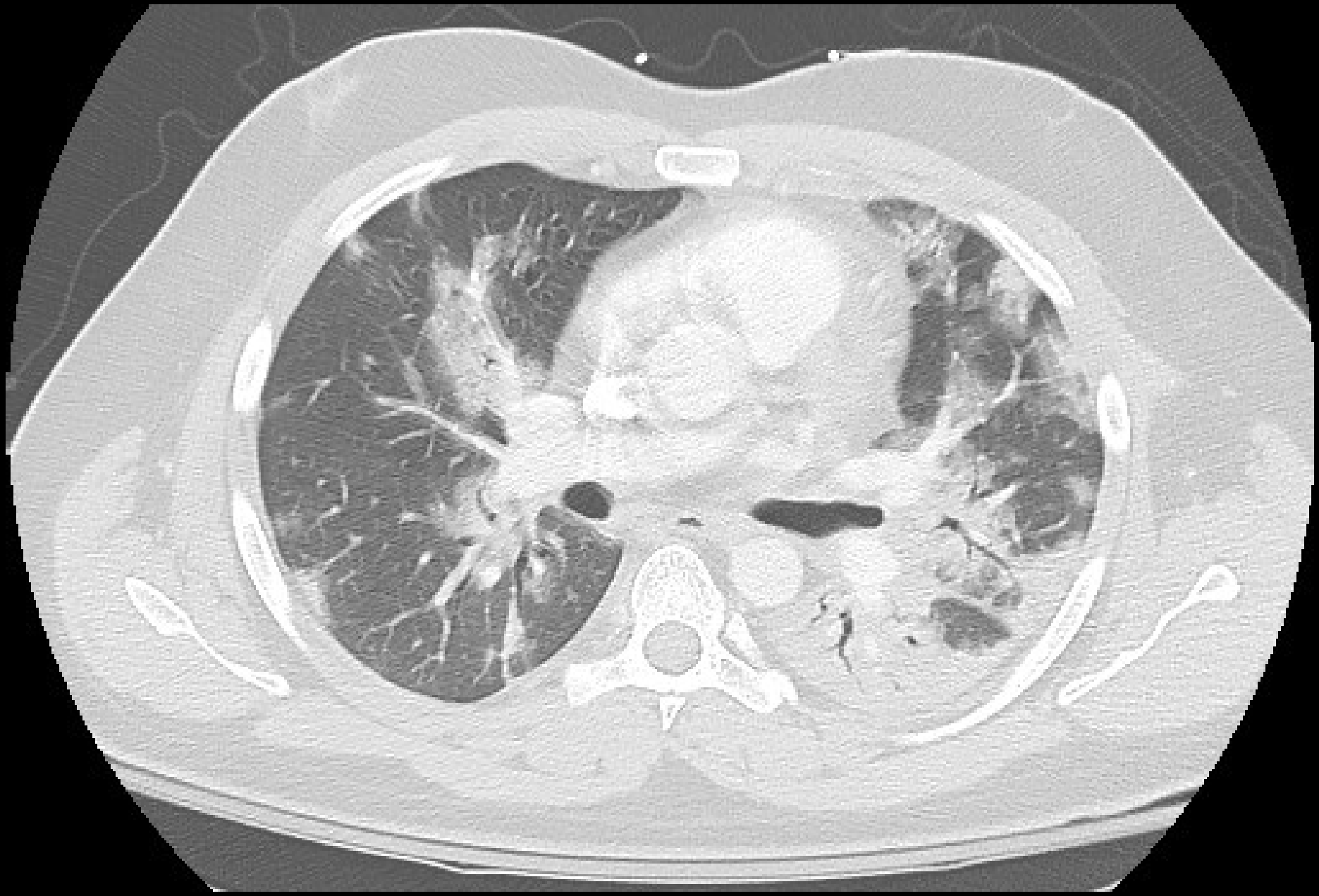


After 3 weeks of therapy with Voriconazole

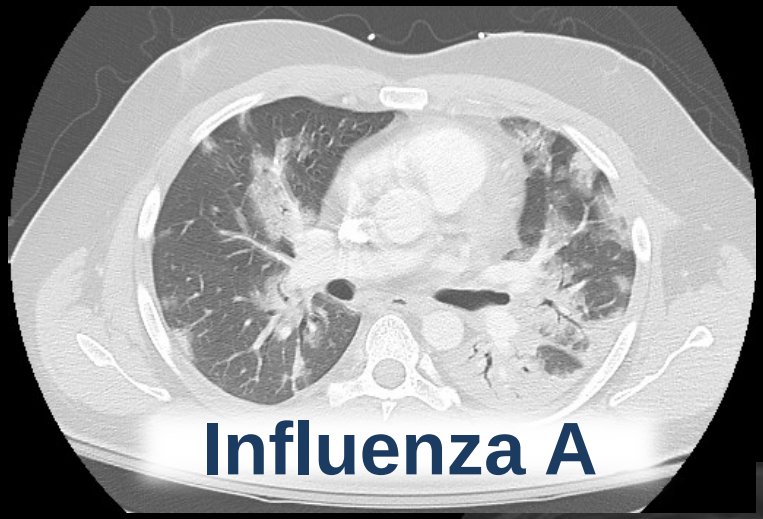


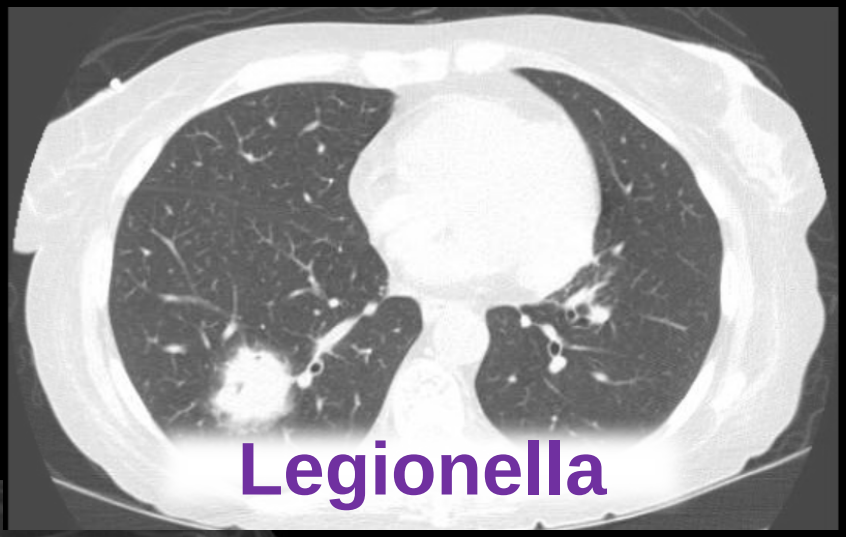





FRED HUTCH

Etiologies of Chest CTs?

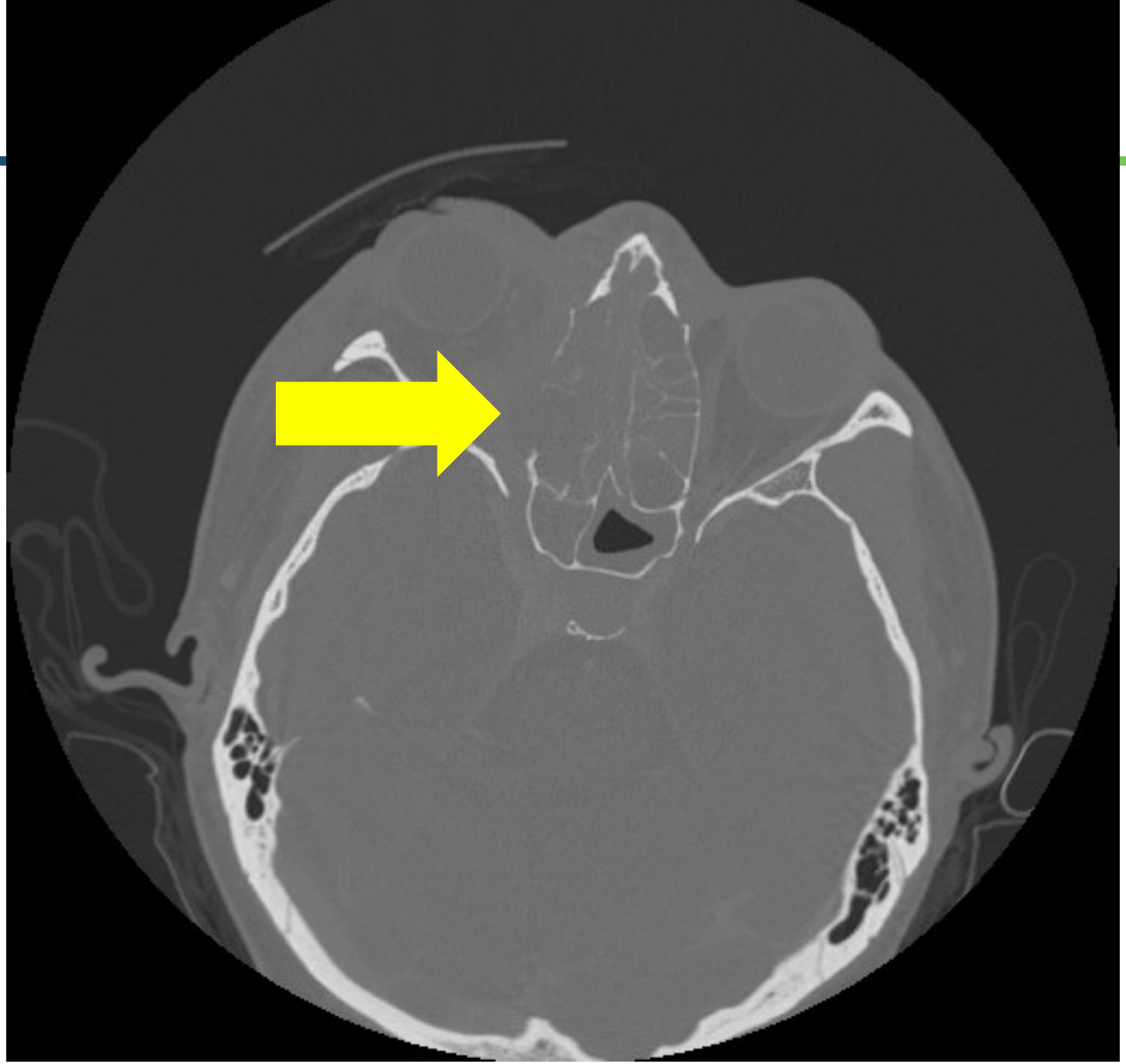




BAL important in diagnosis off pulmonary disease/nodules

Case

- 67 y/o male s/p G-CLAM X 2 with prolonged neutropenia
- Hospitalized with neutropenic fever
- On Cefepime/Vancomycin
- Develops sinus symptoms over 24 hours
- Switched to Meropenem
- Pain and numbness over “cheek”

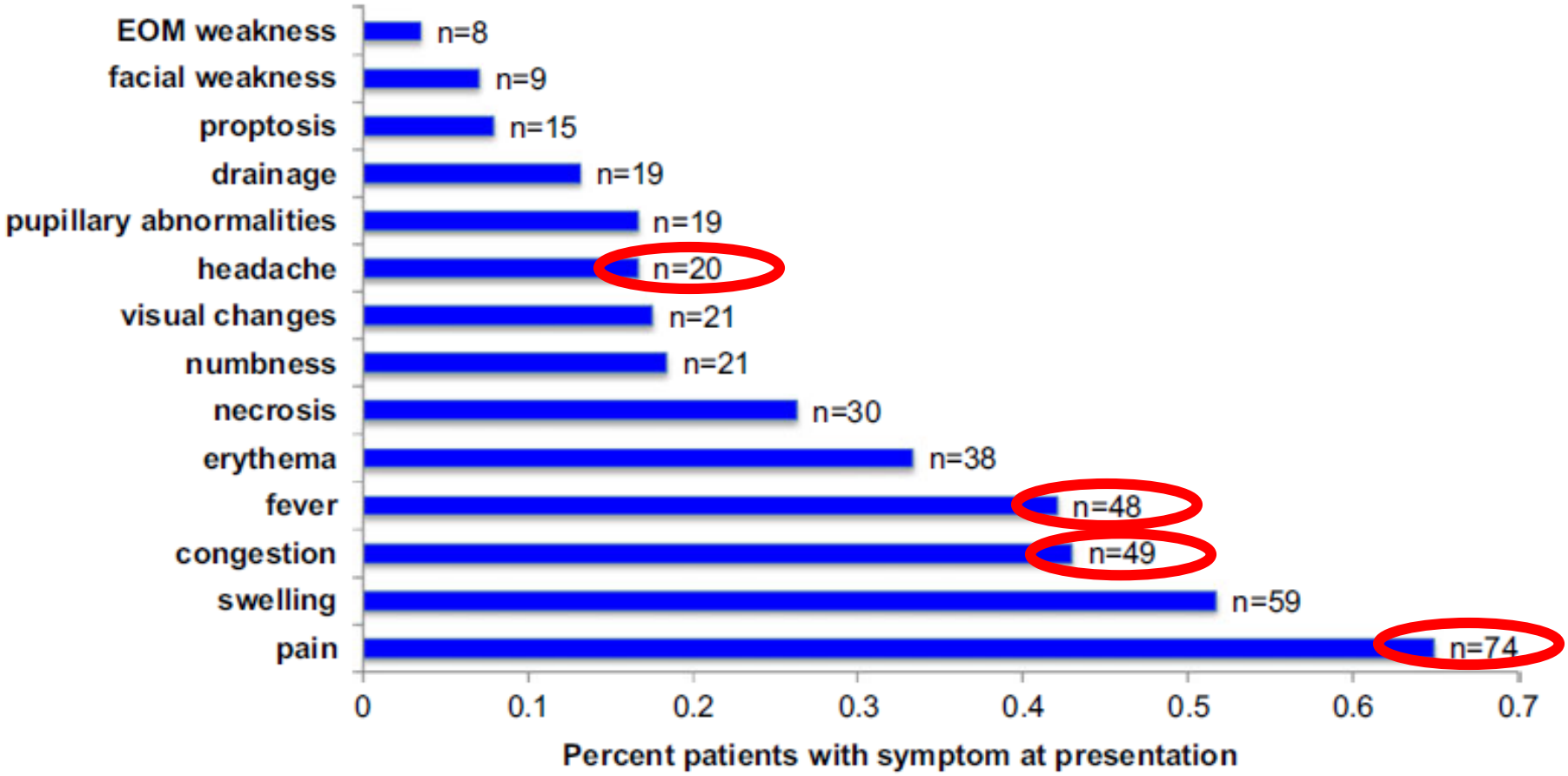


Don’t Forget Fungal sinusitis

- Prevalence 0.5-1.7% of all HCT recipients and leukemia[1,2]
- Etiologic agents:[3]
  - #1 = Aspergillus spp.
  - #2 = Mucorales spp.
  - #3 = Fusarium spp/?
  - Others: *Scedosporium, Paecilomyces, Scopularopsis, Alternaria* [dematiaceous molds], etc.
  - ~3.5% of fungal sinusitis are mixed infections

1. Johnson Am J Rhino 1997
2. Kennedy Oto Head Neck Surgery 1997
3. Wandell Int J of Allergy & Rhinology 2018

Presenting symptoms?



From Wandell Int J of Allergy & Rhinology 2018

Diagnosis/Treatment?

- Diagnosis? Urgent ENT evaluation

  CT of sinuses

- Treatment?

  IV Ambisome +/- Azole therapy

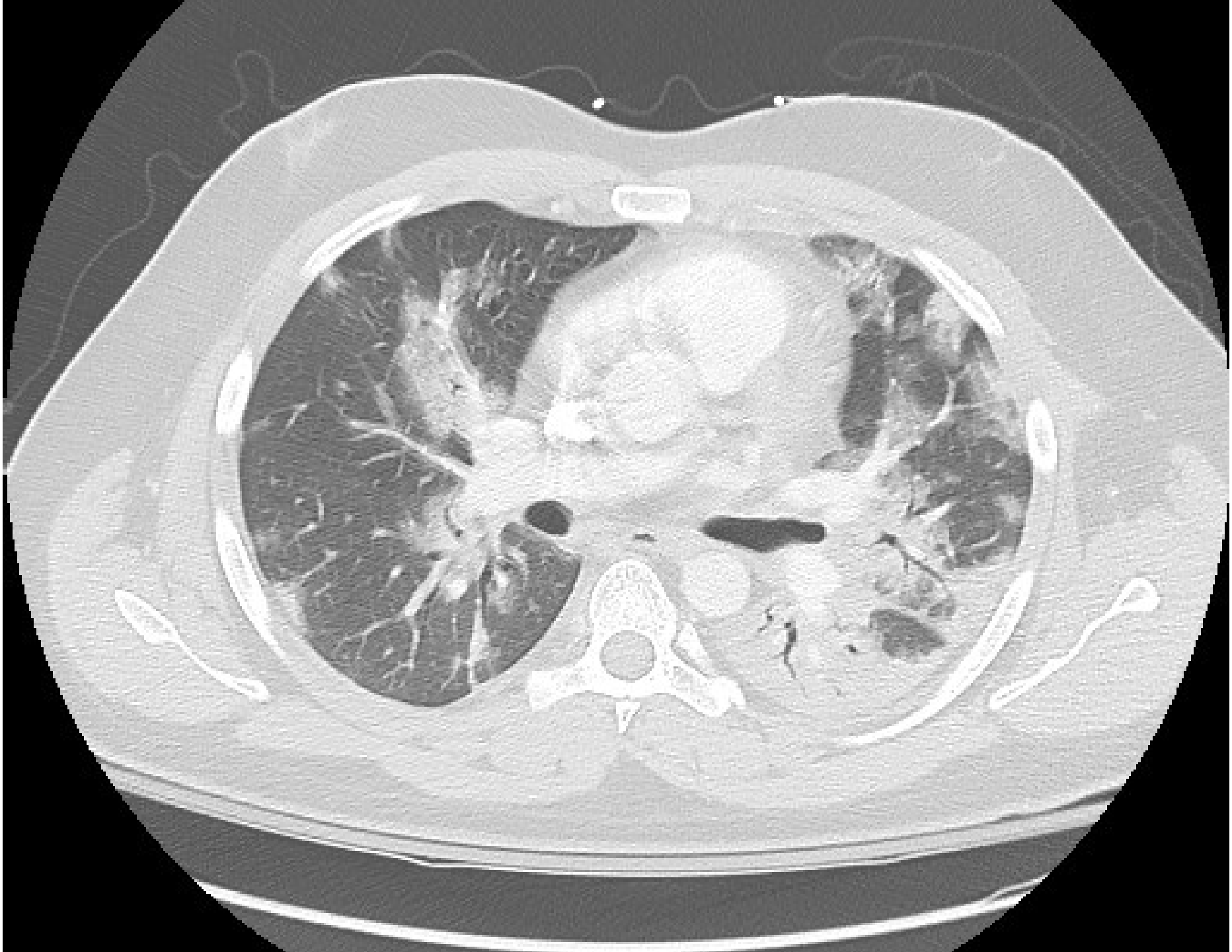
- **SURGICAL debridement and broad spectrum antifungal therapy**

Red Flags for Fungal Sinusitis

- Any CN abnormality
- Facial numbness
- Palatal eschar
- Double vision/vision loss
- Acute sudden MS changes
- Bony erosions on CT/MRI
- Significant Pain
- Prolonged symptoms

Case

- Non-Hodgkin’s Lymphoma
- Autotransplant uncomplicated, 45 days post with neutrophil recovery
- Small children at home
- Fever, myalgias and sore throat 3 days prior to admission
- Develops SOB and presents to ER with O2 sat 87%
- Acute decompensation and sent to ICU
- BAL with bronchoscopy and nasal wash



Case

- Treated with High dose Oseltamivir (150 mg BID), Ribavirin, and Amantidine
- IV Peramavir through compassionate use program
- Intubated/Proned positioning in ICU
- Renal failure dialysis
- In ICU for 3 weeks with ARDS
- Rehabilitation for 4 weeks
- Recovered

Case

- URI symptoms 3 days prior to admission
- Given “Z-pack” by Urgent Care in midst of high level Influenza in community
- Pregnant wife about to deliver, appropriately treated with oseltamivir

Prevention and Early Detection are Critical


Cost of a Transplant = $750,000


Cost of ICU admission = $250-500K
(minimum)

Respiratory Viruses –

(Days 0 to +100 and season dependent)

- Significantly higher frequency of pneumonia & death
- Atypical presentations and rapid clinical progression
- Higher risk of nosocomial transmission (cohorting)
- Persistence (shedding) after primary infection
- Important viruses seen in transplantation:

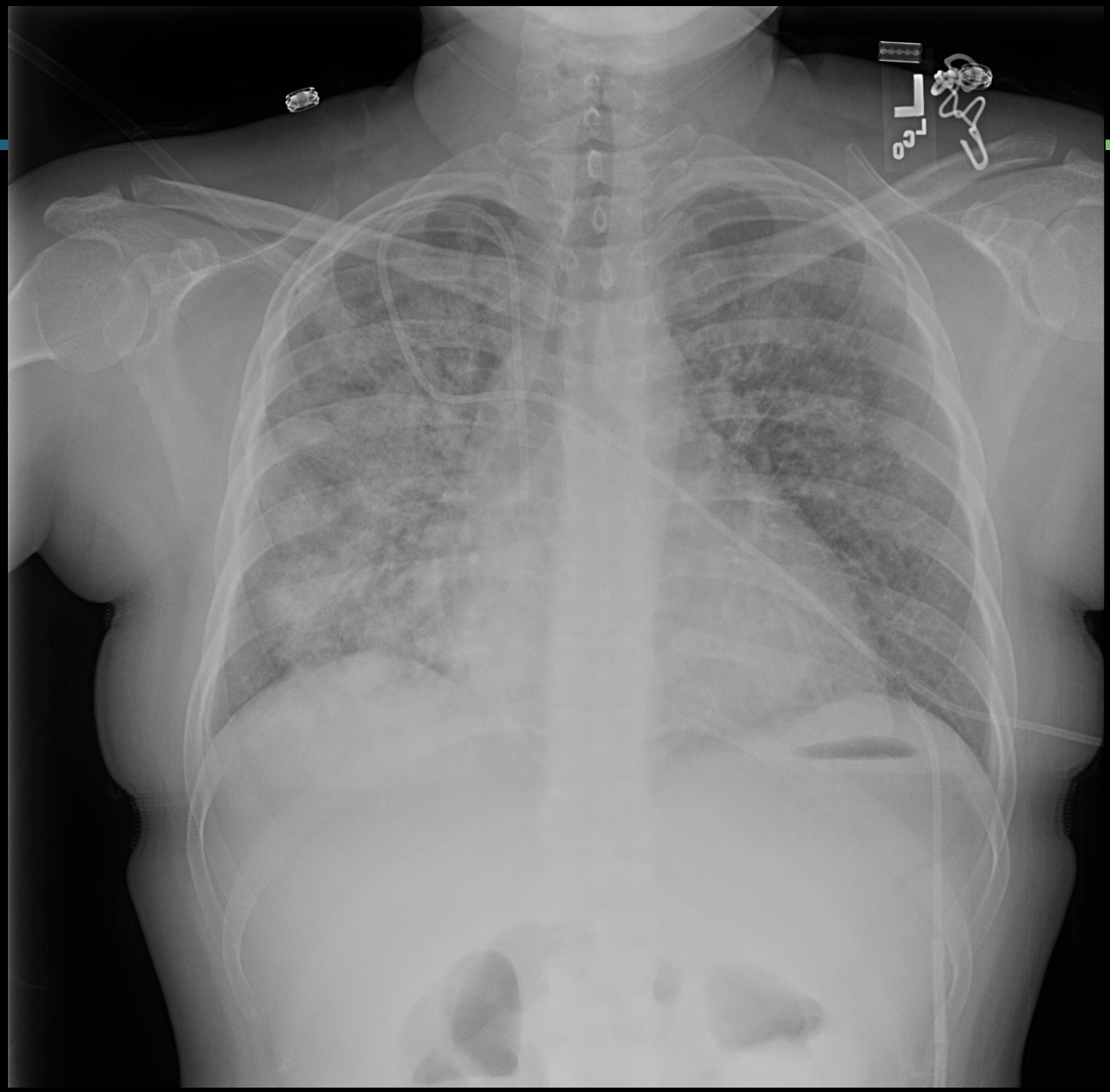
Influenza A/B Parainfluenza Metapneumovirus

Respiratory Syncytial Virus (RSV) Adenovirus

Coronavirus Rhinovirus Bocavirus

SARS-CoV-2

Heikkinen Lancet 2003



Cytomegalovirus (CMV)

- Ubiquitous, latent, herpes virus
- Major factor in determining risk: *What is the Antibody status of recipient?*
- Seronegative recipients with seronegative donors may acquire primary CMV from external sources
- Once CMV infection is established its replication is highly dynamic.
- Invasive disease reduced with routine surveillance and early tx in 1st 100 days
- Treatment Options: Ganciclovir, Valganciclovir, Foscarnet, Cidofovir

1. From Razonable and Limaye, in Transplant Infectious Diseases,3rd Edition.
2. Kalil, et al. Ann Int Med 2005;142:870-80

CMV Prevention Strategies

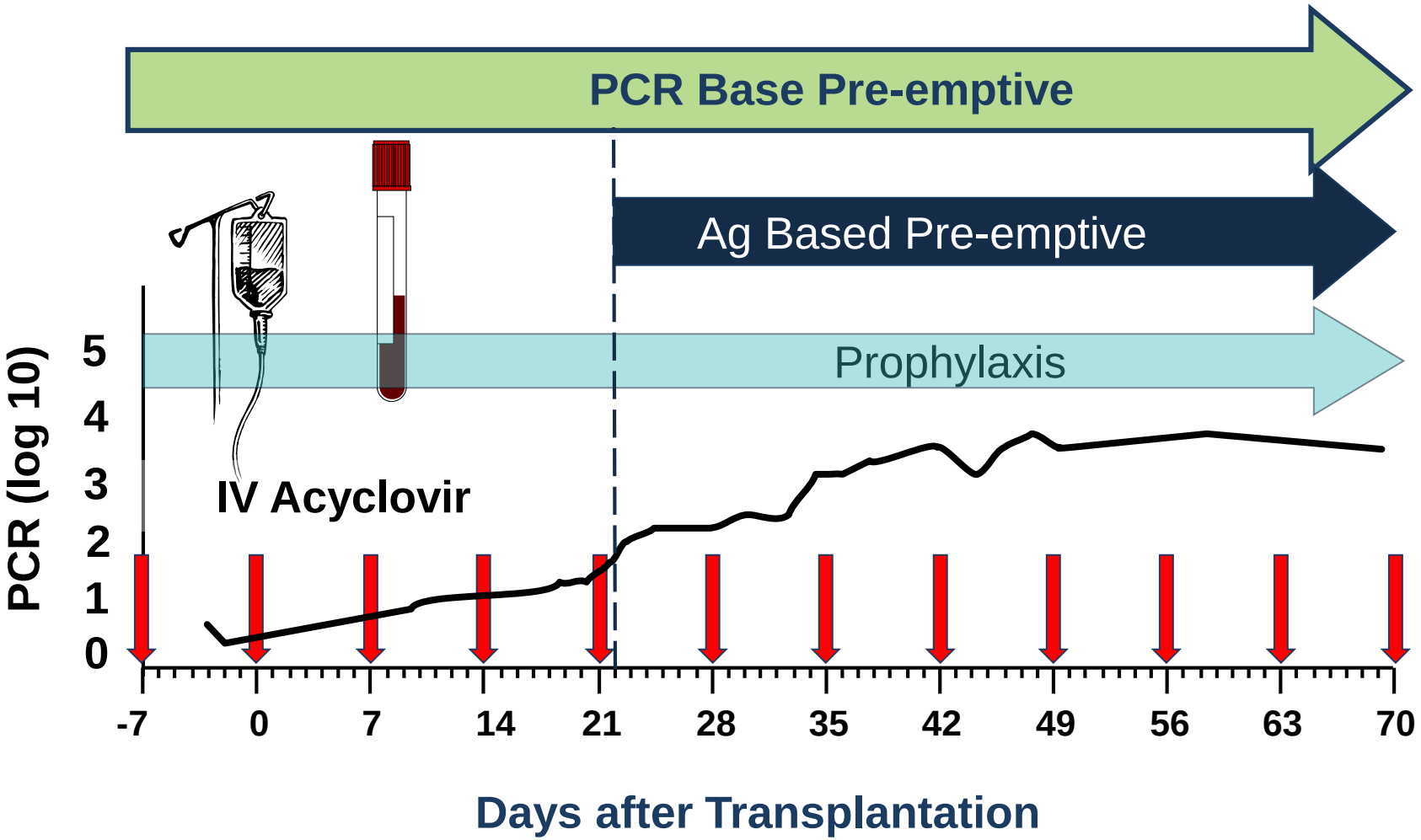
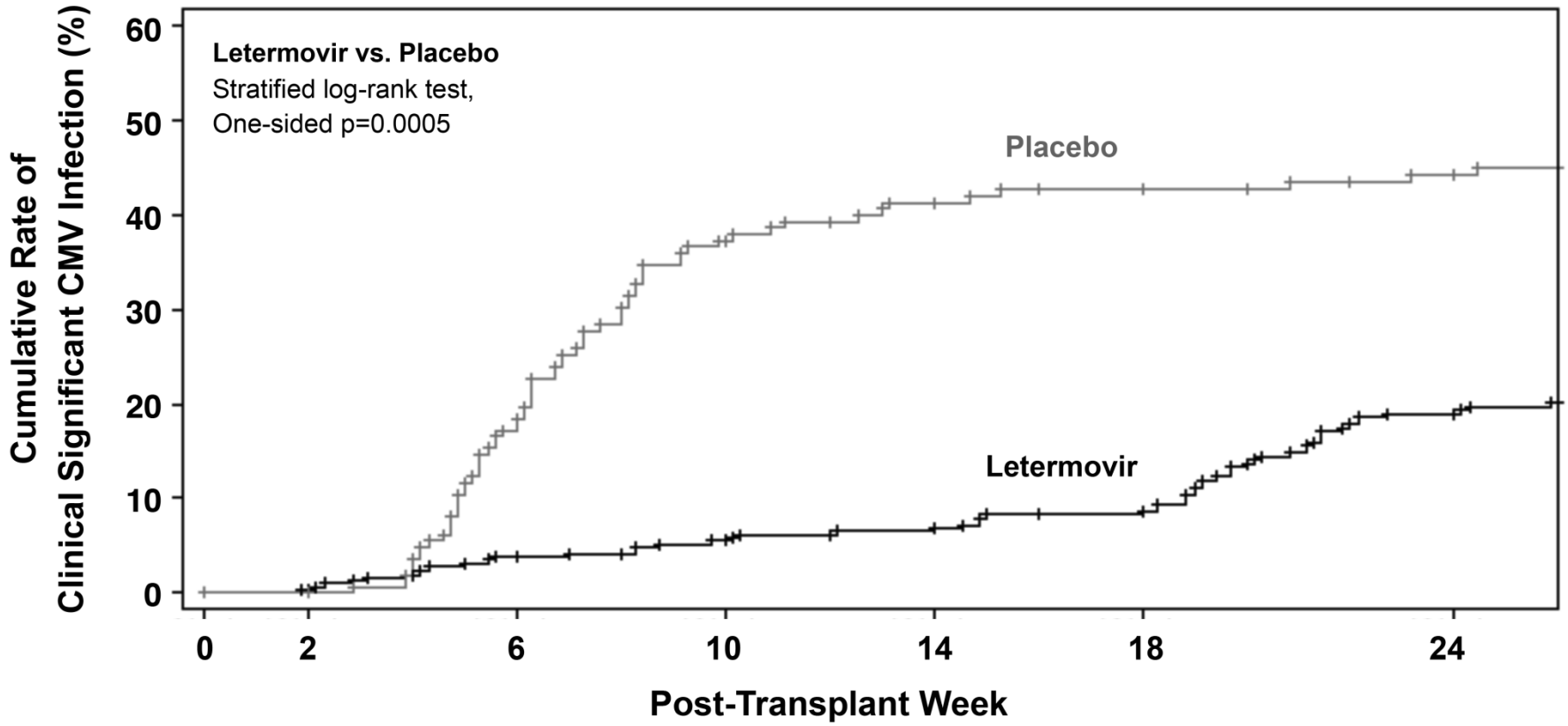


Figure 1. Time to Onset of Clinically Significant CMV Infection

Subjects with undetectable CMV DNA at Randomization



Letermovir	325	320	299	279	270	254	212
Placebo	170	169	135	96	85	77	70

Subjects at risk

Marty NEJM 2017

Direct Effects of CMV Infection

CMV Viral Syndrome

- Fever, malaise, myalgias
- Neutropenia, Leukopenia, thrombocytopenia, and other laboratory abnormalities

Tissue Invasive Disease

- Hepatitis
- Pneumonitis
- Colitis
- Carditis
- Nephritis
- Pancreatitis
- Retinitis

Late Post-Transplant Infections (>100 days)

Late Infections?

- CMV
- Herpes zoster
- Hepatitis A, Hepatitis B, Hepatitis E
- Encapsulated bacterial infections (pneumococcus)
- Fungal infections (intra-abdominal Mucor, Cryptococcus)
- EBV associated PTLD

Late Post-Transplant Infections (>100 days)

- Allotransplant patient presents at day 234, with fever, RUQ pain
- Chemistry panel, low Na
- CBC elevated WBC (13K)
- LFT's start high, but continue to rise (AST 2145 and ALT 3546)
- Hep A / Hep B and Hep C negative
- US of abdomen demonstrates small amount of ascites
- Patient's pain controlled with increasing amounts from morphine PCA
- Develops delirium

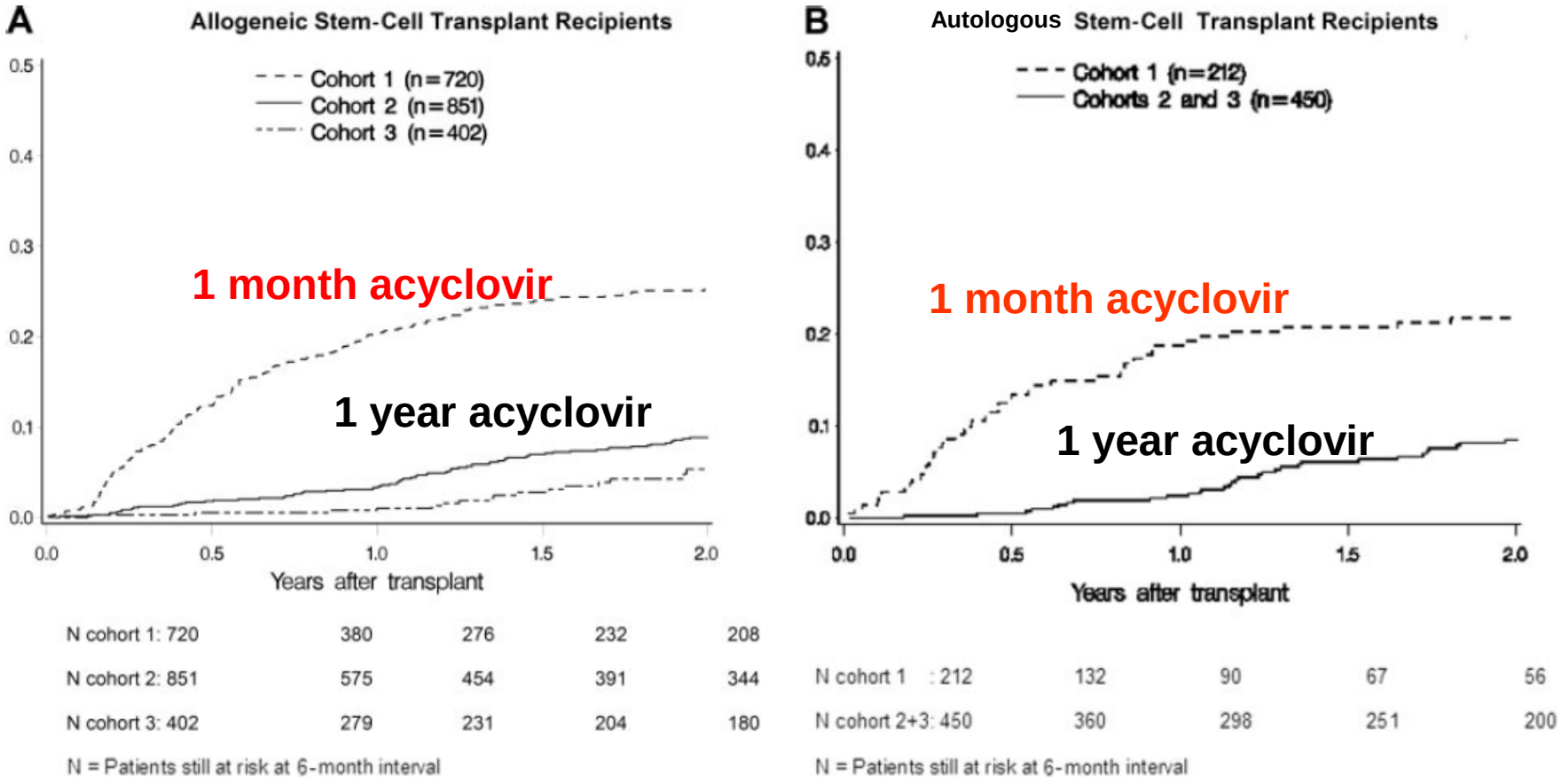
Day 2

Abdominal/Visceral Zoster

- Rare presentation of Herpes Zoster
- Triad of **severe abdominal pain, hyponatremia and elevated transaminases**
- Often presents without associated zoster rash initially
- VZV PCR diagnostic method of choice
- Treatment with high-dose acyclovir
- If treatment delayed may be associated with high rate of mortality
- Prevented with use of standard acyclovir prophylaxis

Varicella Zoster Prevention

Acyclovir Prophylaxis Post-HCT Prevents HZ after 1st year



From Erard Blood 2007;110(8):3071-7

Case

- 37 y/o female with AML, s/p G-CLAM
- Levofloxacin and voriconazole for prior pulmonary nodules
- Neutropenia for 12 days
- Develops neutropenic fever and found to have CoNS, treated with Vancomycin and Levofloxacin
- Recurrent fever at day 27
- Complains of cough and chest pain

Mucorales spp.

- Fungi of the order Mucorales
- Ubiquitious mold found in dirt, decaying vegetation, decaying fruit and bread
- Grow very rapidly in petri dishes “blow lid of plates”
- Linked to severe disease
- Disease typically occurs in patients with high-risk features: trauma, high-iron levels, prolonged neutropenia, and steroids,
- Breakthrough for patients on azoles (particularly voriconazole)

Treatment

- Surgery
- Antifungal agents = particularly IV Ambisome
- Surgery
- Surgery
- Surgery


cm
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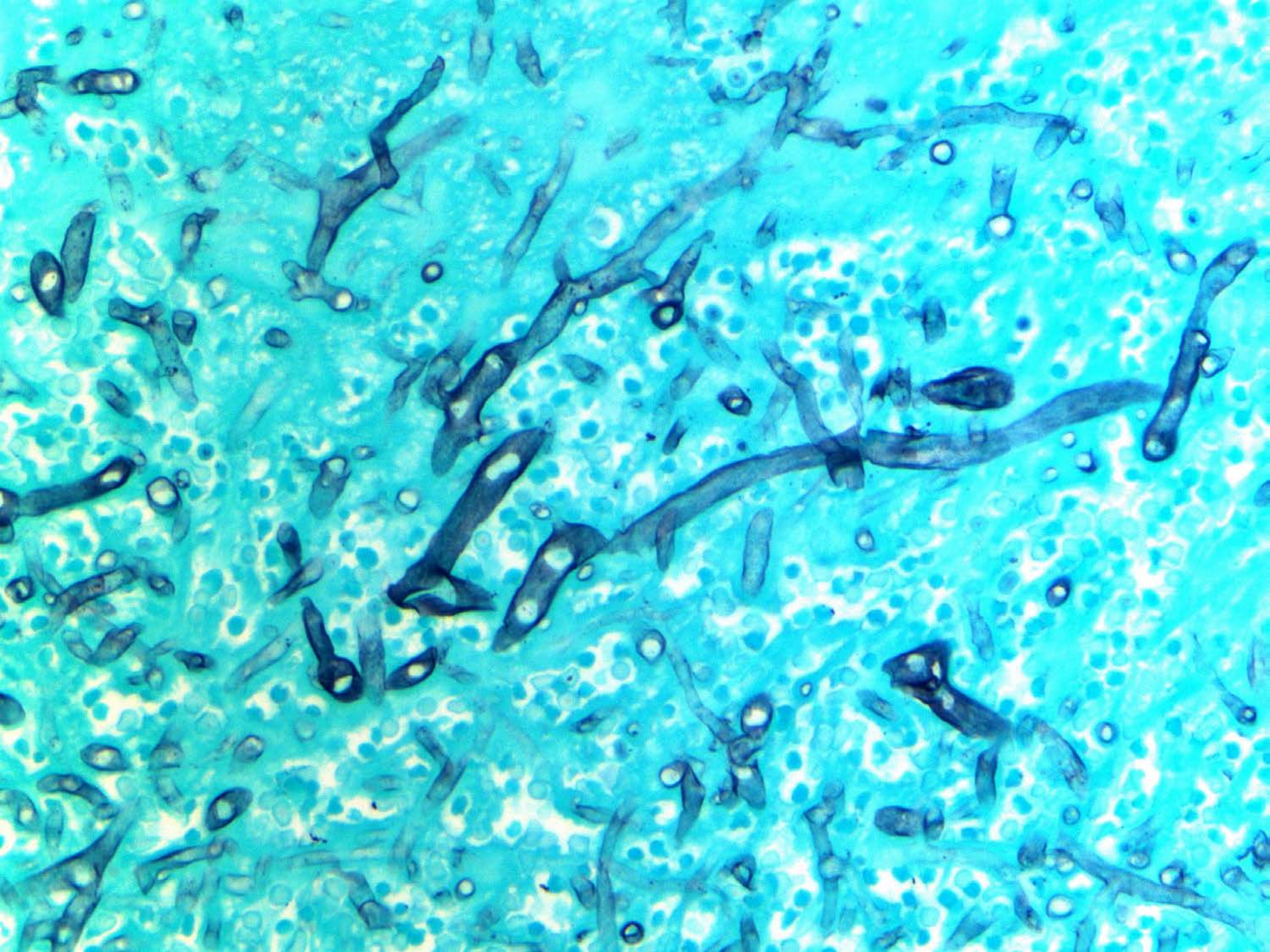
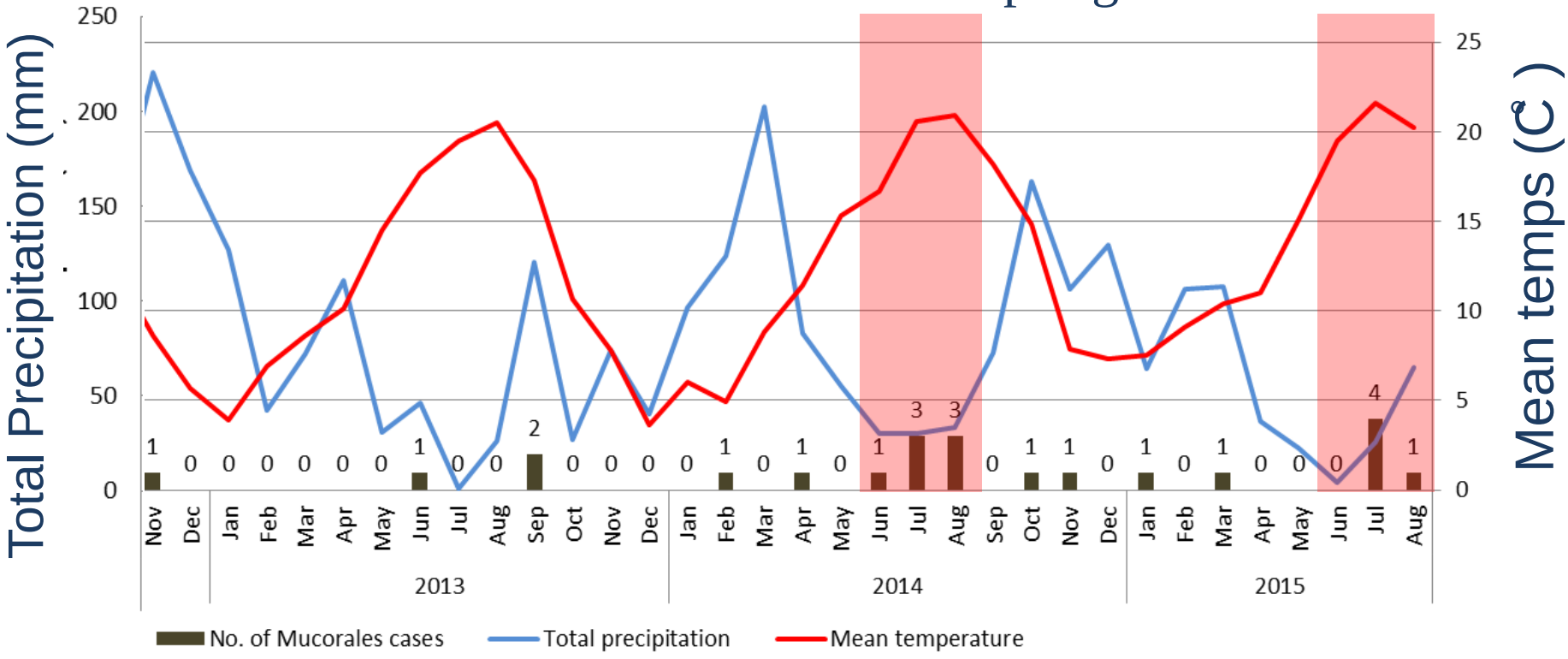
5



Temperature and Mucorales?

Summer = 5.67 cases per 10,000 inpatient days

Fall = 4.10 Winter = 1.94 Spring 1.3



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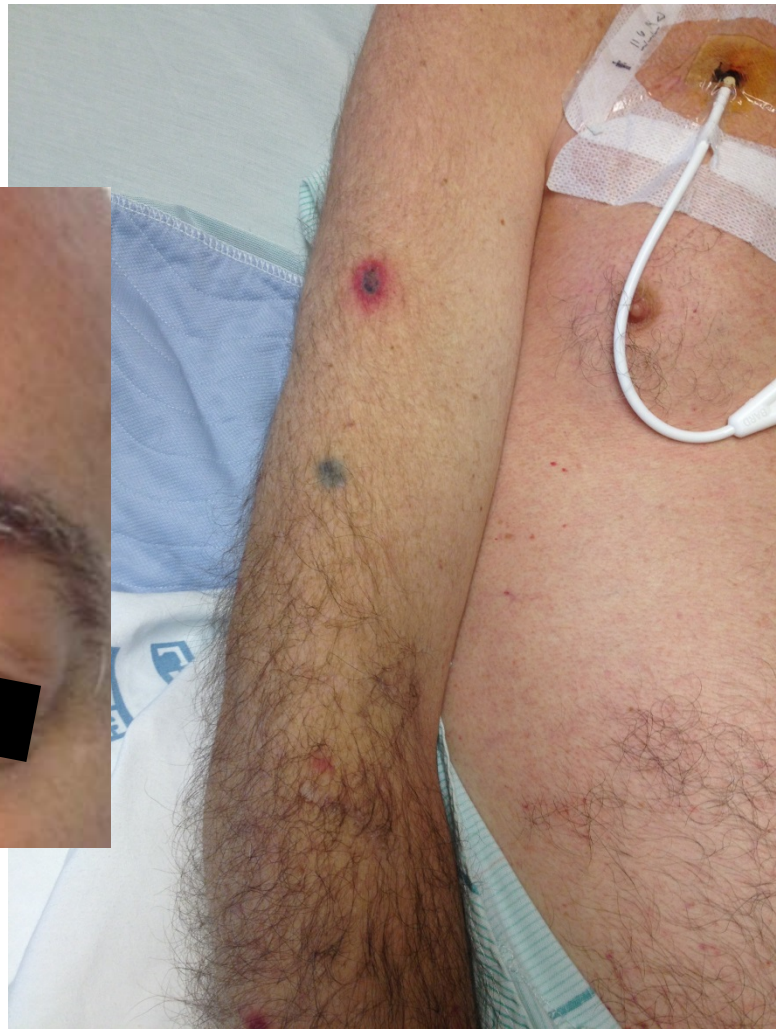
Case

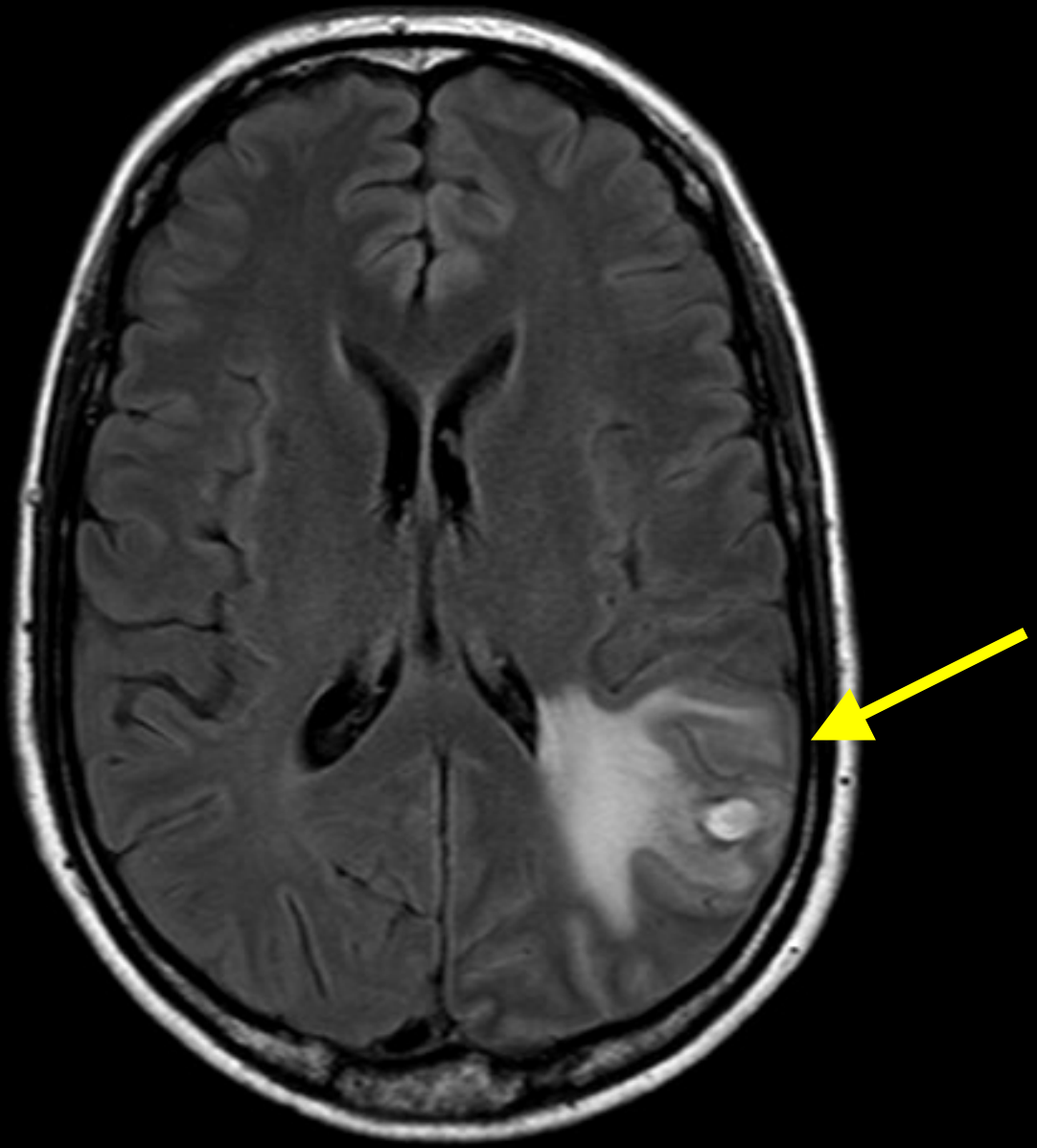


Antifungal briefly

- **Fluconazole** – Candida prophylaxis in HCT
- **Posaconazole** – standard prophylaxis for AML therapy
- **Voriconazole** – first choice for most Aspergillus species
- **Isavuconazole** – Aspergillus/Mucorales, less drug and drug/drug side-effects
- **IV liposomal Ampho B** – Breaktrough molds

56 y/o male with MM s/p autotransplant

- Had fever at home and then increasing confusion
- Developed grand mal seizure in ER during evaluation
- Transferred with abnormal brain lesion, on Ceftriaxone and Vancomycin
- Cultures reported as GNR/GPR in blood by outside hospital



Listeria monocytogenes

Epidemiology

Uncommon infection in the general population, transplant patients at increased risk

Listeria is anaerobic gram positive rod found commonly in soil, water, decaying vegetation and animals

Foodborne listeriosis is most common source for transplant recipients

In a CDC study 64% of people with listeria had at least one food source in their fridge that grew listeria[1]

Most common sources were ready-eat-foods, soft cheeses and deli meats

http://flickr.com/photo/80507002@N00/1879607602

Photo by Andre Karwath from Wikicommons

From wikicommons

1. Pinner, et al. JAMA 1992;267:2046-50

Cannabis? New Risks?

How often is MJ contaminated with mold?

- Study in Neth. found that 100% of all MJ + for fungus, compared to 64% in cigarettes[1]
  - Estimated to be 300 to 50,000 times more CFU/g mold on MJ compared to commercial cigarettes
- MJ cigarettes from 26 chronic users, found 73% grew *Aspergillus spp*, and spores easily passed into air sampler during smoking process[2]
  - 52% positive for Aspergillus precipitins in their blood, compared to 10% in controls
  - *Mucorales spp* found less frequently

Verwiej JAMA 2000 2. Kagen NEJM 1981 3. Moody NEJM 1982

New agents: Infections / Non-ID syndromes

- Bortezomib – VZV, CMV?
- Ruxolitinib – HBV, Cryptococcus, MTB
- TK inhibitors – CMV infection (e.g. disatinib)
- Ibrutinib – Aspergillus/Fungi
- Eculizimab – Meningococcal disease
- Idelalisib – CMV / PJP

New agents: Infections / Non-ID syndromes

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- Non-infectious complications:
  - *PI3K inhibitors – pneumonitis*
  - *CAR-T cells – cytokine release syndrome*
  - Immune checkpoint inhibitor – diarrhea

Non-infectious Causes of Fever

Drug toxicity

Drug allergy

Drug fever

Underlying malignancy

Sweet's syndrome

Pulmonary embolism

Alveolar hemorrhage

Transfusion reaction

BOOP/IPS

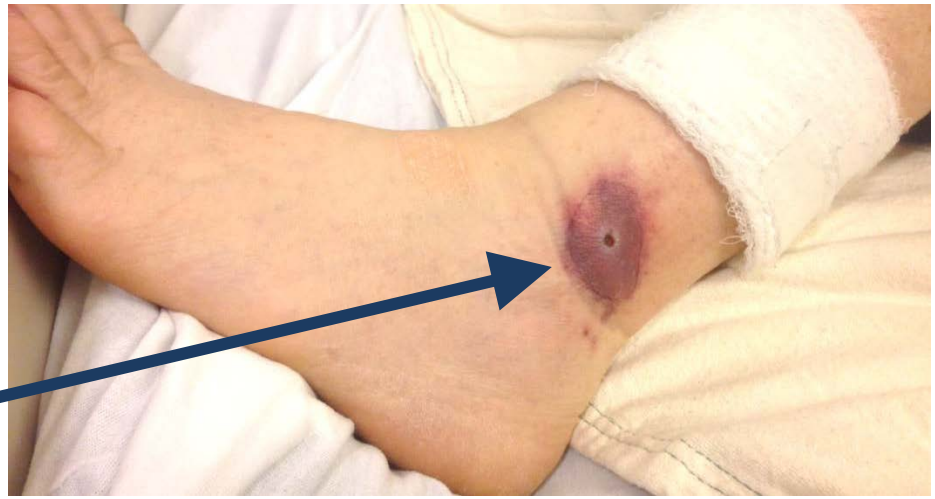
GVHD / Rejection

Don’t Forget Non-infectious Causes of Fever

Don’t Forget Non-infectious Causes of Fever

Sweet’s syndrome

Disseminated Aspergillus



Questions?

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