Infections in cancer and hematopoietic stem cell transplant recipients

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Seattle Cancer Care Alliance
Fred Hutch · Seattle Children's · UW Medicine

Some slides adapted from Steven Pergam, 2020

Objectives and Outline

1. Understand risk factors for infection in cancer and HCT recipients
2. Understand how prophylactic antibiotics/antivirals/antifungals are used
3. Understand the approach to neutropenic fever
4. Recognize novel antimicrobials in advanced stages of clinical trials
5. Tackle cases involving
    A. Bacteria
    B. Fungi
    C. Viruses
    D. Infectious mimics

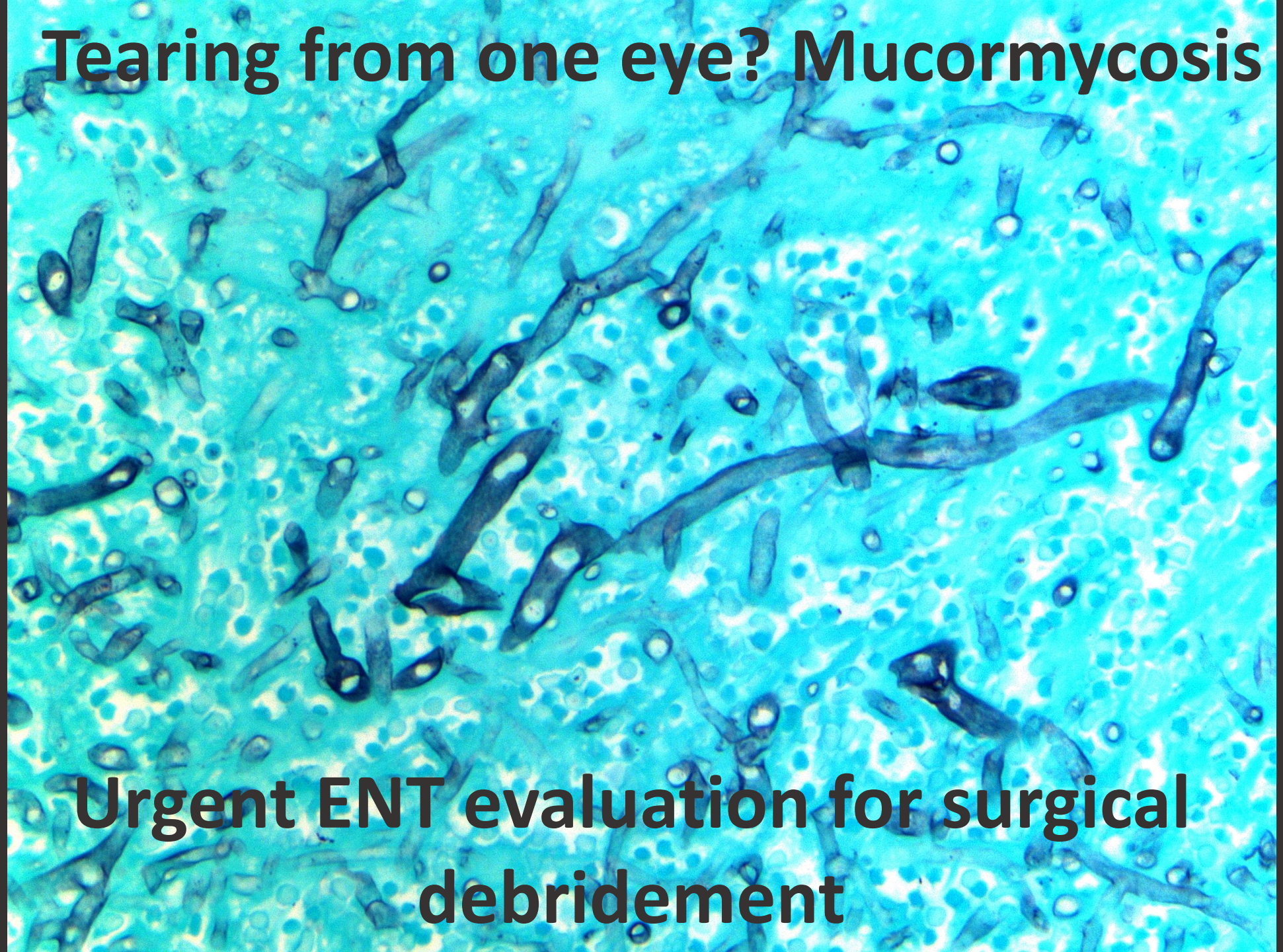
Principles of infections in immunocompromised hosts

1. Timeline for infection with major pathogens is relatively consistent
2. Common things are common but common things can present atypically
    A. Highly virulent pathogens can have mild presentations
    B. Pathogens with traditionally low virulence can rapidly progress and be fulminant
3. Unique, rare, opportunistic infections
4. **Pay close attention to symptoms (constant vigilance)**

Tearing (epiphora) from just one eye?

Image from Getty Images

Tearing from one eye? Mucormycosis



Urgent ENT evaluation for surgical debridement

1. Risk factors for infection

Medication-related immunosuppression

- Radiation
- Cytotoxic chemotherapy
- Steroids
- Calcineurin and mTOR inhibitors
- MMF
- Monoclonal antibodies
  - Alemtuzumab
  - Rituximab
  - TNF inhibitors
- Proteosome inhibitors
- Kinase inhibitors
- Immunotherapy

Additional risks for infection

- Lymphopenia, neutropenia
- Delayed T-cell recovery
- Chronic GVHD
- Mucosal barrier injury
- Transfusions
- Prior antibiotic use, colonization with MDROs
- Gastric acid suppression
- Prolonged hospitalization
- Central lines, TPN
- Renal/liver dysfunction
- Splenectomy
- Age, obesity
- Iron overload

Mechanism of infection: Outside-in

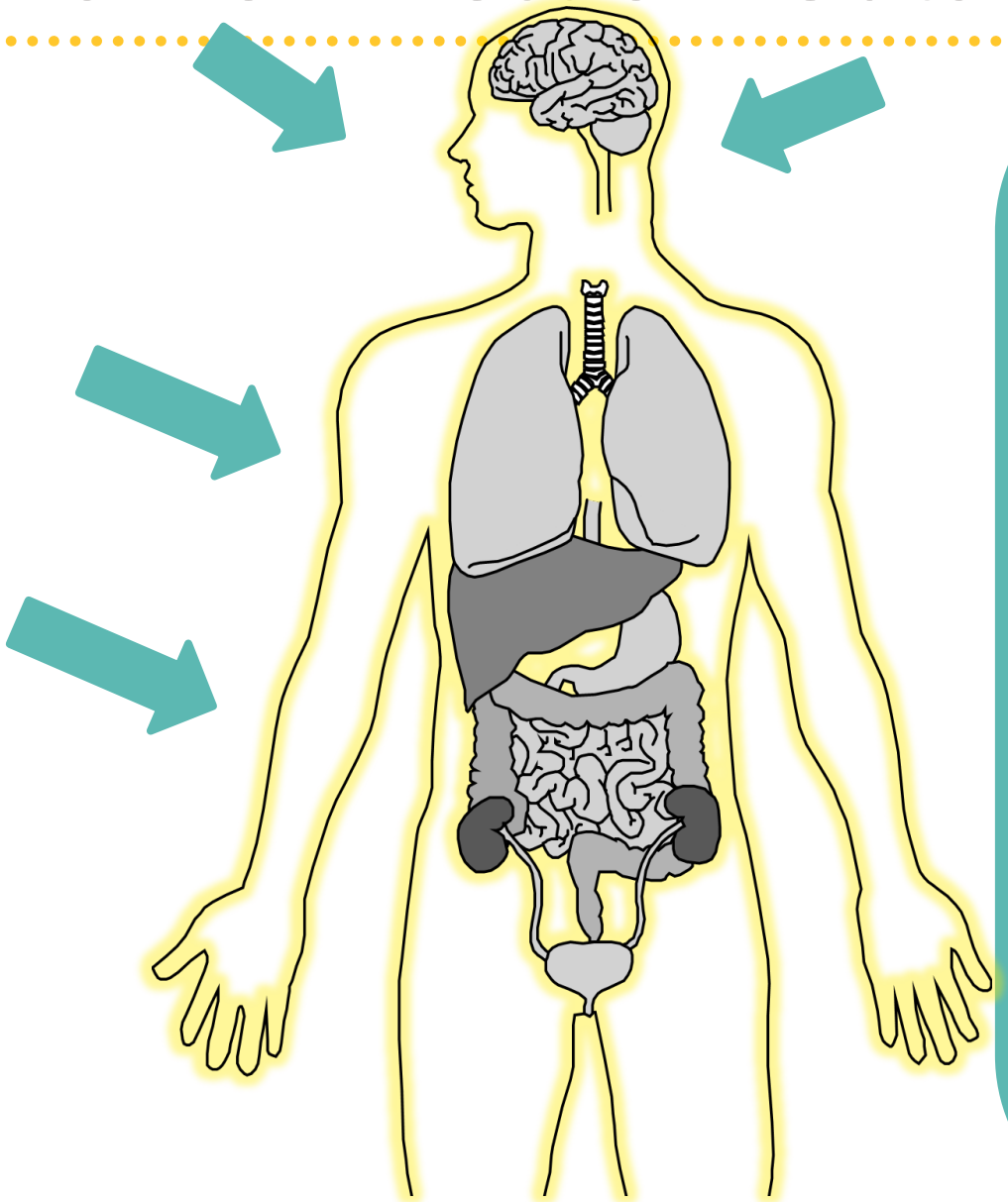


Image by Kyoko Kurosawa

External Microbial Agents

Viruses

Influenza
RSV
Paraflu
Adenovirus
Norovirus
Enteroviruses
Legionella

Bacteria

VRE
MRSA
Resistant GNR
Nocardia
C Difficile

Parasites

Toxoplasma

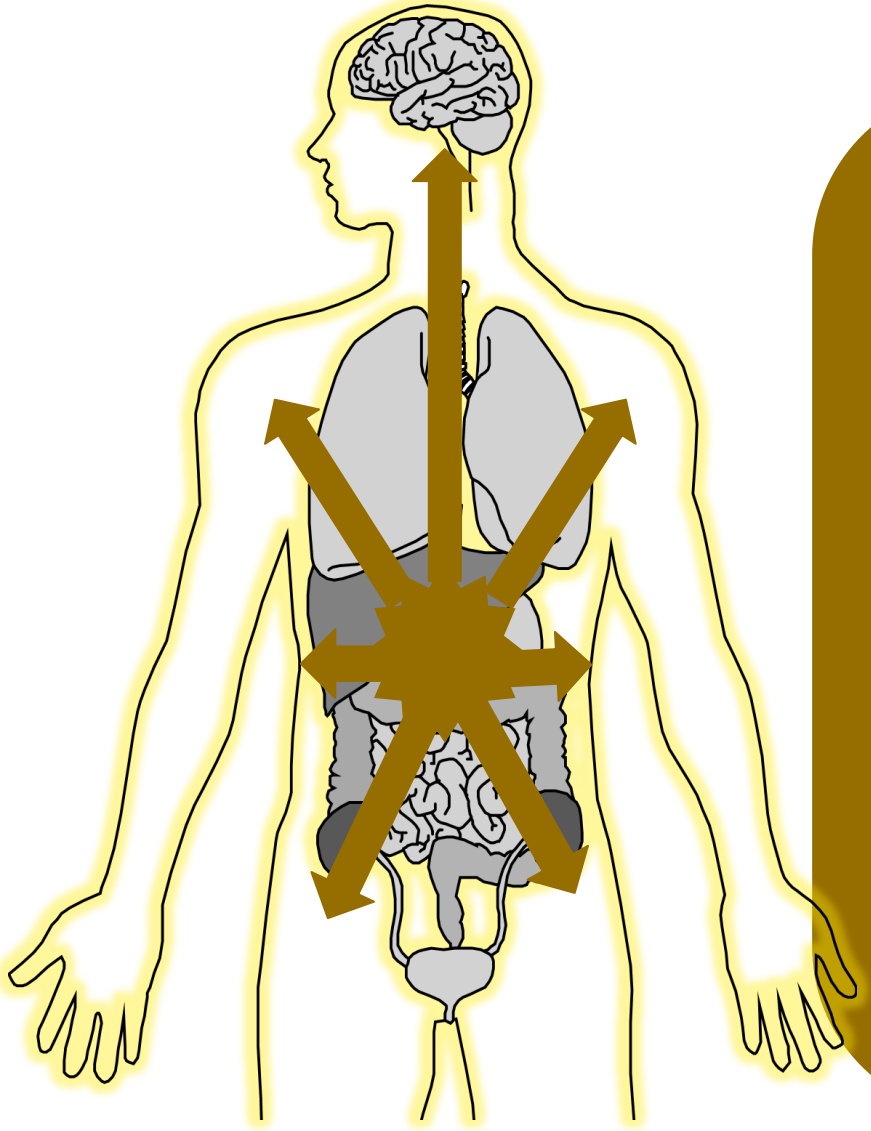
Fungi

Aspergillus
Mucorales
Cryptococcus
PJP

Inside-out (enemy within)

nature medicine
LETTERS
https://doi.org/10.1038/s41591-018-0202-8

Precision identification of diverse bloodstream pathogens in the gut microbiome Tamburini, 2018



Internal Microbial Agents

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

Fungi
- Candida
- Cocci / Histo

Bacteria
- Enteric GNRs
- Skin flora
- TB
- Strep/oral flora

Parasites
- Strongyloidiasis
- T. cruzi
- Toxoplasma

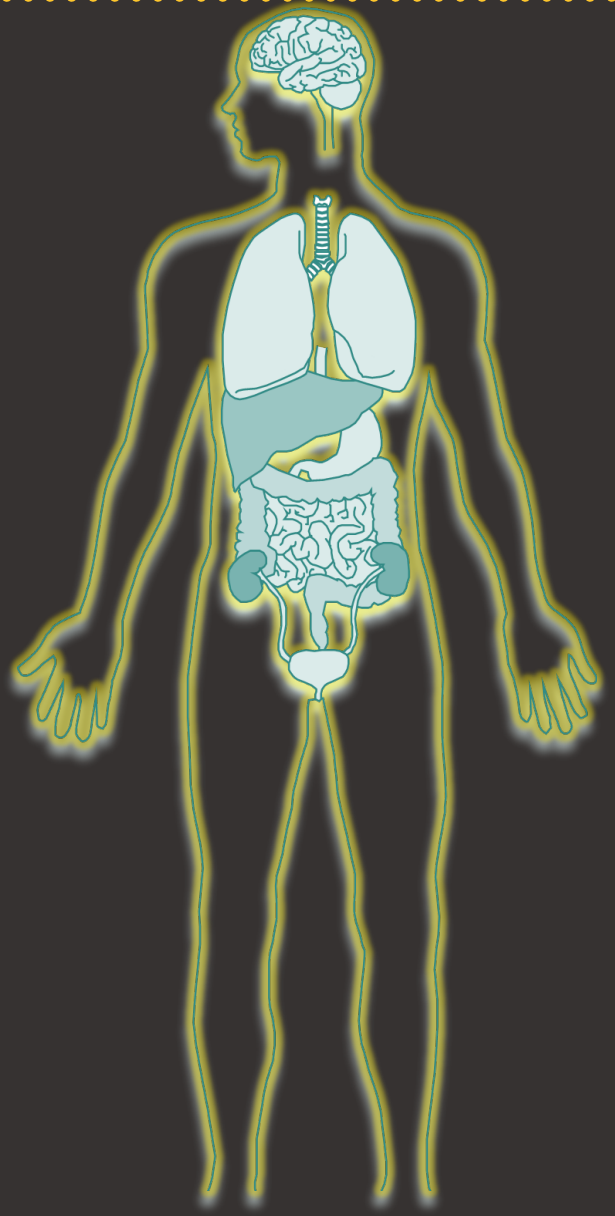
Location, location, location

Bacteria, fungi can infect any site

Sinuses/Lungs
PJP
Respiratory viruses
Herpesviruses (CMV)
Adenovirus
Toxoplasmosis

Liver
Hepatitis viruses
Adenovirus
Herpesviruses

Kidneys/Bladder
Adenovirus
BK virus



CNS
Herpesviruses
JC virus
West Nile virus

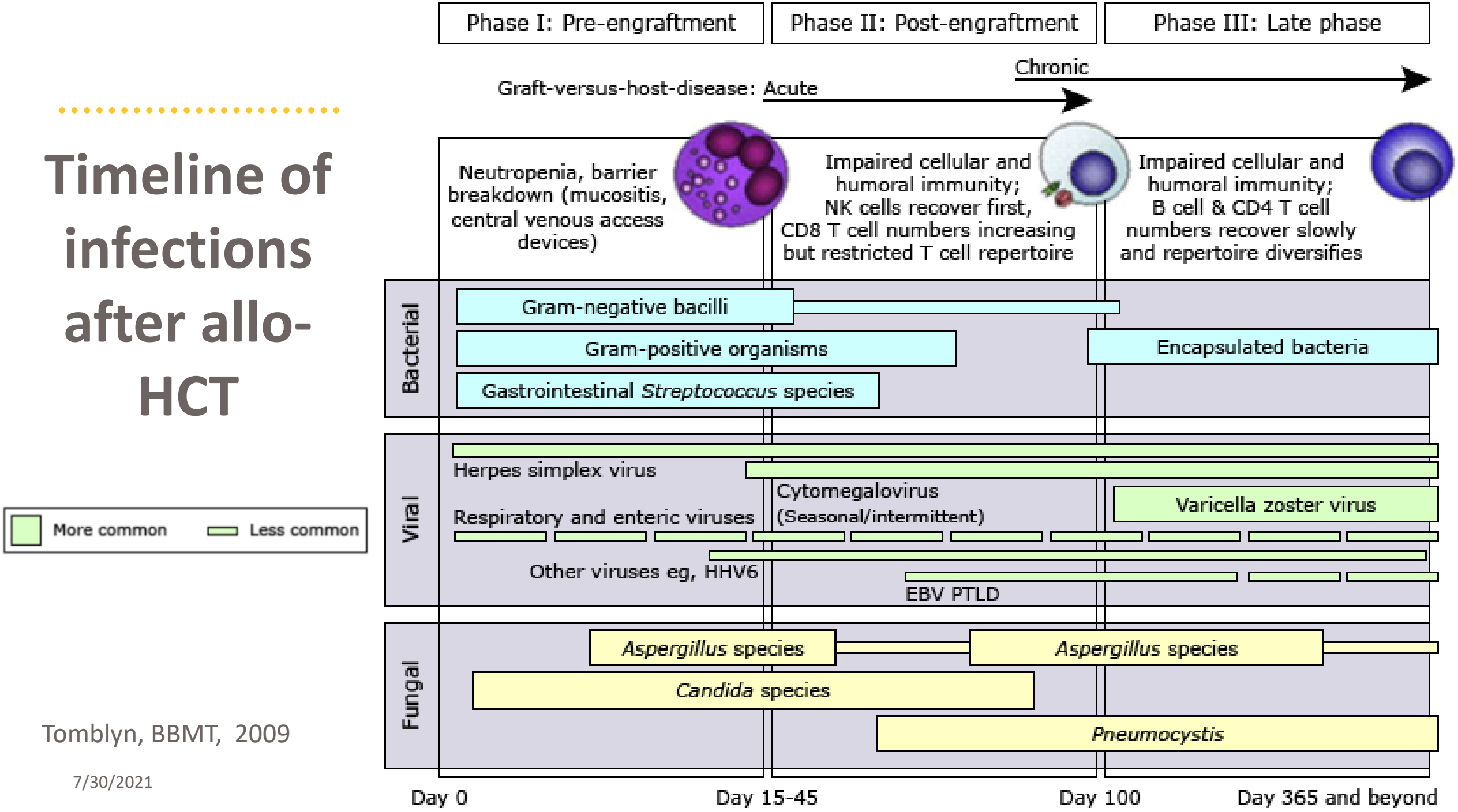
Gut
Adenovirus
Norovirus
Herpesviruses (CMV, HSV)
Parasites/Protozoa

Skin
HPV, Molluscum
Herpesviruses (VZV, HSV)

Consider timing

- How long neutropenic?
- Early during inpatient management?
- After returning to the community?
- After completing prophylaxis?
- During prophylaxis?
- Recent chemotherapy/what type?
- Ongoing GVHD?
- Steroid use?

Timeline of infections after allo-HCT



Tomblyn, BBMT, 2009

Prevention / prophylaxis in brief

- **Bacteria**
  - Neutropenia – Fluoroquinolones (ceftazidime, cefpodoxime, amox/clav if unable to tolerate)
  - Chronic GVHD (encapsulated bacteria) – Bactrim / pen VK
- **Viruses**
  - HSV/VZV – (Val)acyclovir
  - CMV - Val(ganciclovir / foscarnet / high dose (val)acyclovir / letermovir
- **Fungal**
  - Yeast/Mold – Fluconazole / posaconazole / voriconazole / isavuconazonium
  - Pneumocystis – Bactrim (1st line) / dapsone (test for G6PD) / atovaquone (high-fat)

Special situations

- Toxoplasmosis - Bactrim
- Hepatitis B – Lamivudine / entecavir / tenofovir
- Strongyloides – Ivermectin (travel history is key)
- Latent tuberculosis – INH (exposure history is key)

Are you sure your patient is taking their:

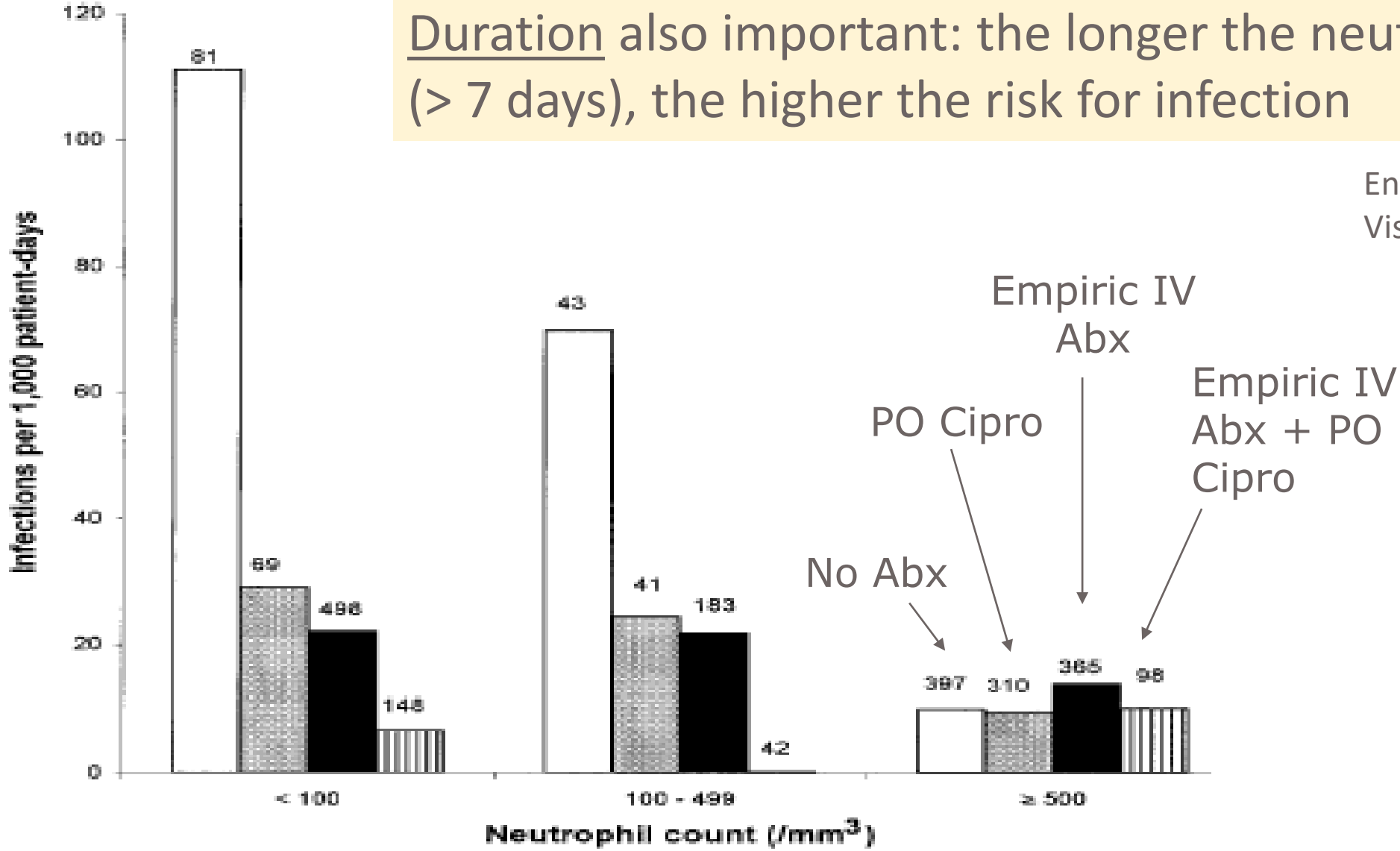
- Bactrim?
- Acyclovir?
- Anti-fungal?

Image from marrowmovement.com

Pre-engraftment prophylaxis: Why 500?

Duration also important: the longer the neutropenia (> 7 days), the higher the risk for infection

Engels, CID, 1999
Viscoli, CID, 2005



Case: Fever

57-year-old man status post MURD HCT (day +15)

Neutropenic

On levofloxacin prophylaxis

Fever to 101.5°F

What are common causes of fever early post-transplant?

Most common infectious causes of fever early post-transplant

Bacteria in general are the most common:

- Gram positive bacteremia is now the most common, especially with mucositis, account for 60%
  - S. epidermidis
  - Viridans strep
  - S. aureus
- Gram negative rods (including Pseudomonas), especially with gut GVHD, mucositis, or steroids account for 40%

Fungi: Candida, mold

Viruses: HSV, VZV, CMV, respiratory viruses

Gudiol, Clin Microbiol Infect, 2013

Case: course continued

- Over the next 48 hours, he develops hypotension and requires transfer to the ICU
- Empiric antibiotics?

- **Earlier administration of antibiotics associated with improved survival**
- Admit high-risk patients for IV antibiotics
  - ❑ Cefepime
  - ❑ Ceftazidime (does not cover gram-positives)
  - ❑ Meropenem or piperacillin/tazobactam in patients with:
    - history of multi-drug resistant GNRs
    - intra-abdominal infection
  - ❑ Consider adding aminoglycosides if there is concern for multi-drug resistant GNRs
  - ❑ Consider adding vancomycin if severe mucositis, line infection, or skin/soft tissue infection
    - Daptomycin/Linezolid can be used against resistant gram positives but remember daptomycin does not enter the lungs.

Prolonged neutropenic fever – what next?

- Median time to defervescence after initiation of empiric antibiotics in HCT recipients is five days
- Vancomycin or other gram-positive coverage can be stopped after 2-3 days if no evidence of gram-positive infection.
- Consider empiric antifungal coverage in
  - High-risk neutropenic patients
  - Expected neutropenia > 7 days
  - Persistent fever after four to seven days of broad-spectrum antibiotics and no identified source

Case: Cultures

- Blood cultures begin to grow GNRs

- What are the most common GNRs in HCT recipients?

  - ❑ **E. Coli**
  - ❑ Enterobacter
  - ❑ Klebsiella
  - ❑ Pseudomonas
  - ❑ Stenotrophomonas – *intrinsically resistant to meropenem*! Treatment of choice is with TMP/SMX

Image from cannabisbenchmarks.com

Case: Weed

28-year-old man with AML status status-post allogeneic transplant

Day +22

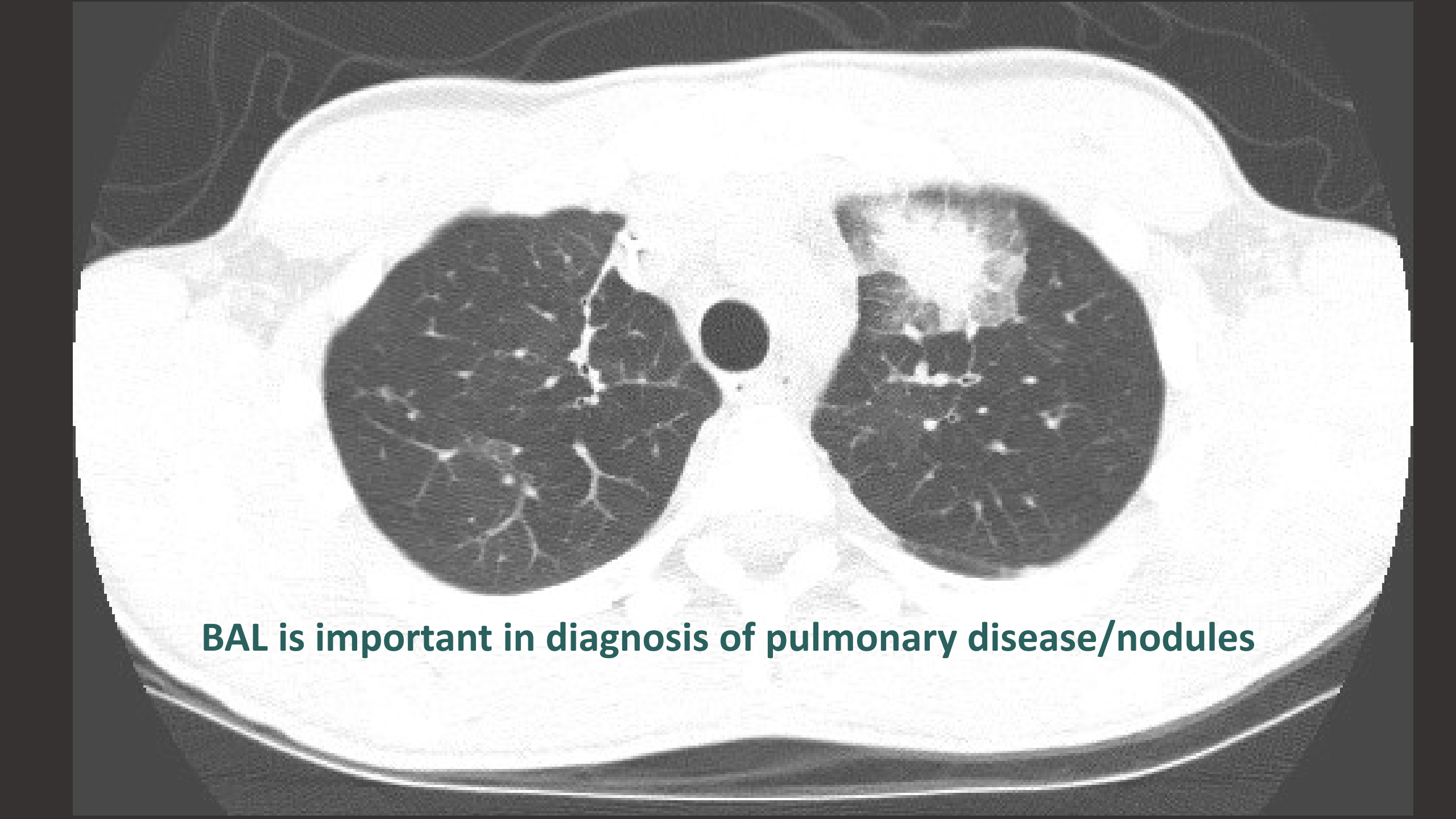
Admitted with neutropenic fevers

Work up negative

Empirically treated with IV cefepime

Had been on fluconazole prophylaxis

Develops dry cough and left sided pleuritic chest pain

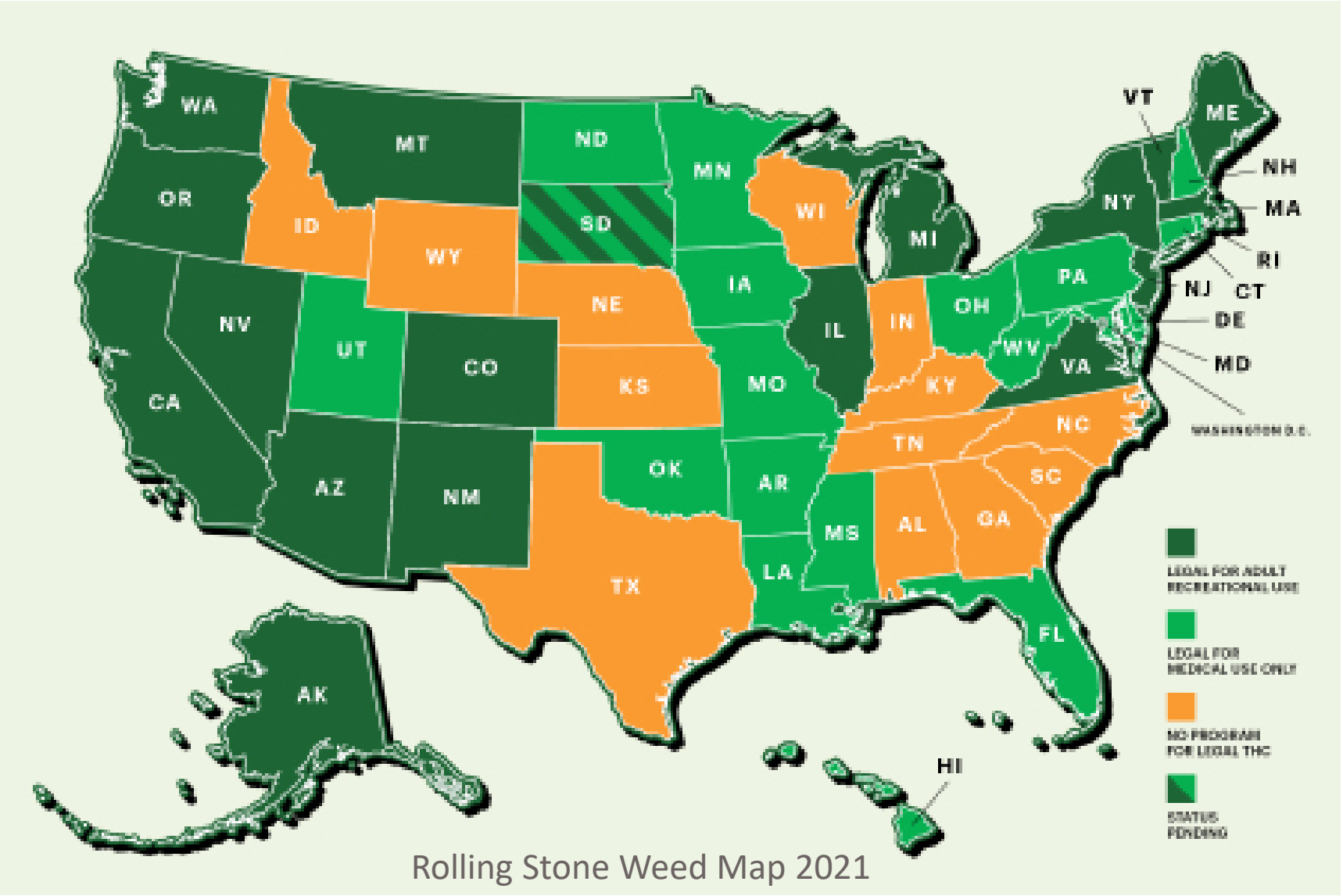


BAL is important in diagnosis of pulmonary disease/nodules

- Galactomannan
- PCR
- Culture
- Histology

Cannabis in the US

- 100% of marijuana and 64% of cigarettes contaminated with mold
- Up to 100,000 times higher cfu of mold per gram in marijuana compared to cigarettes
- Most commonly Aspergillus species



Rolling Stone Weed Map 2021

Verwiej, JAMA, 2000
Kagen, NEJM, 1981
Moody, NEJM, 1982

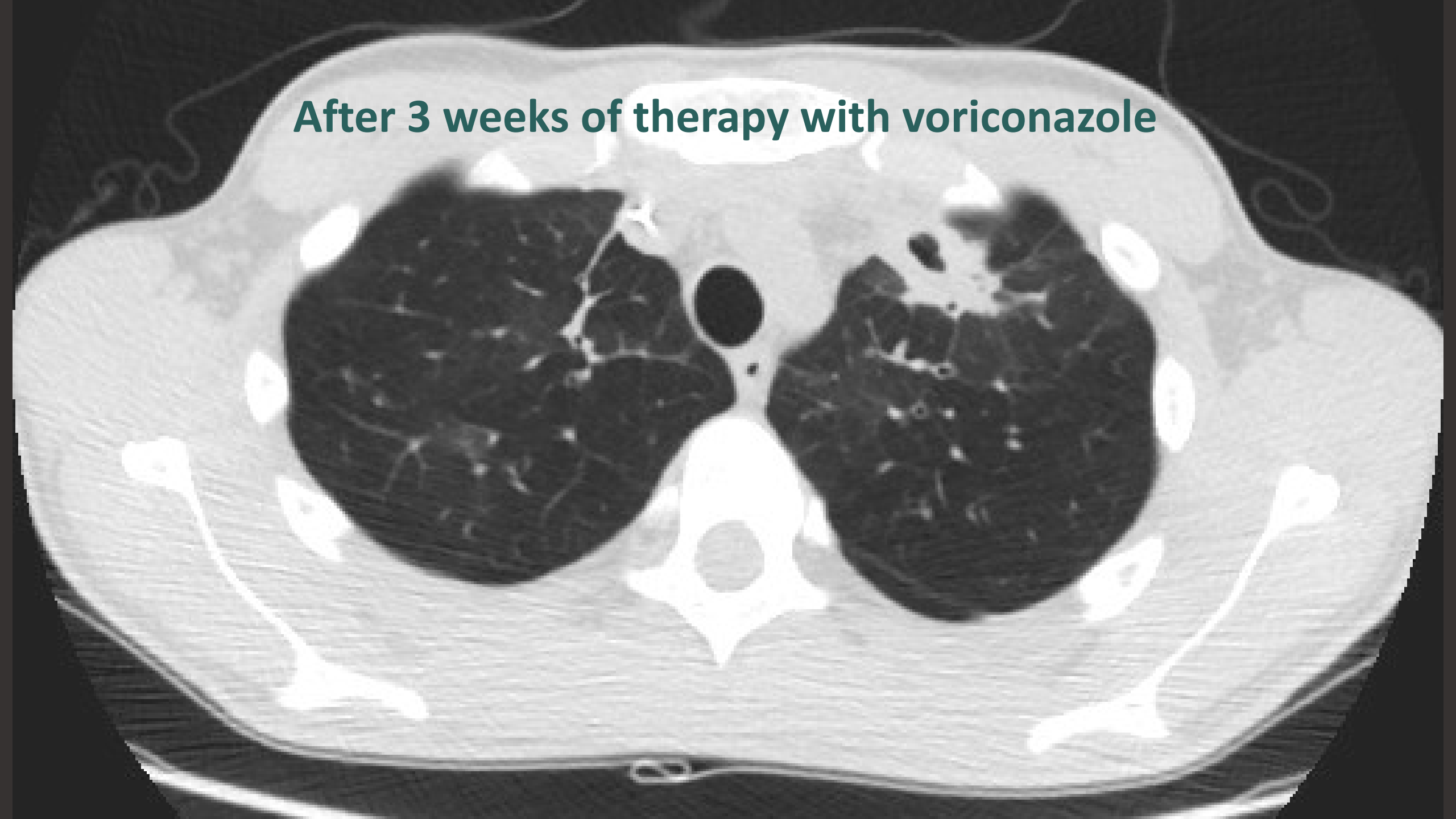

After 3 weeks of therapy with voriconazole

Image from craftygeek.co.uk

Case: What if it wasn’t Aspergillus?

37-year-old woman with AML status-post induction chemotherapy

Levofloxacin and voriconazole prophylaxis

Neutropenic for 20 days

Develops neutropenic fevers, cough, and chest pain

Mucormycosis

- Infections caused by fungi of the order Mucorales (Rhizopus, Mucor, Rhizomucor)
- Ubiquitous mold found in dirt, decaying vegetation/fruit/bread
- Grows rapidly in petri dishes – "*blows the lid off the plates*"
- Occurs in high-risk patients
  - Trauma
  - Iron overload
  - *Prolonged neutropenia*
  - *Steroids*
  - Diabetes
- Fluconazole and voriconazole do not cover

Treatment

Surgery

Surgery

Surgery

Ambisome


cm 1 2 3 4 5

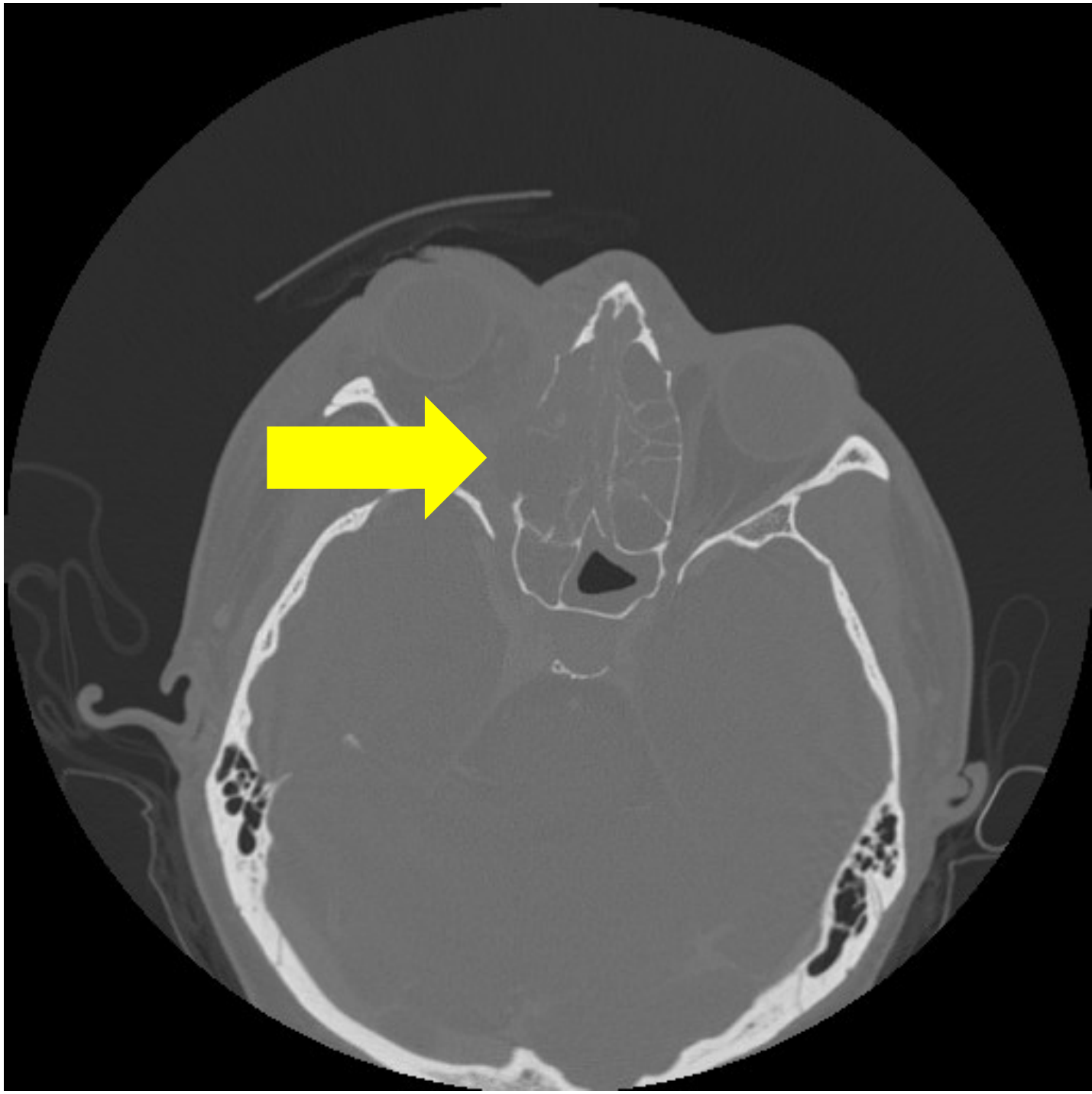
Don’t forget about fungal sinusitis

Red flags

- Any cranial nerve abnormality (facial numbness, diplopia, vision loss)
- Mental status change
- Severe sinus pain
- Palatal eschar
- Bony erosions on CT/MRI

Urgent ENT referral for surgical debridement

Palatal lesion?



Antifungals briefly

- Micafungin – Candida (including resistant Candida species)
- Fluconazole – Candida and Cryptococcus
- Voriconazole – first choice for Aspergillus
  - Check levels, hallucinations, and fluorosis
- Posaconazole – active against Aspergillus and molds, used commonly as prophylaxis in AML
  - Check levels
- Isavuconazonium – active against Aspergillus and molds
  - No levels to check, fewer side effects, fewer drug/drug interactions
- Liposomal amphotericin – used for Mucorales and breakthrough mold infections
  - *Scedosporium, Aspergillus terreus, and some Fusarium are resistant*

What to do about resistant molds? Novel antifungals to look out for

Phase 3 studies

- Rezafungin: resistant Candida / phase 3 trial testing prophylaxis against Candida, Aspergillus, and Pneumocystis in HCT recipients
- Ibrexafungerp: resistant Candida / PO and IV formulations
- Oteseconazole: Candida and Mucorales / minimal drug-drug interactions

Phase 2 studies

- **Fosmanogepix**: new class / resistant Candida, Aspergillus, Scedosporium, Fusarium, Mucorales / PO and IV formulations / few side effects
- Encochleated amphotericin: Candida and Aspergillus / PO formulation / better tolerated
- Olorofim: new class / Aspergillus, Fusarium, Scedosporium (*not Candida or Mucorales*) / PO and IV formulations / few side effects

Rauseo, OFID, 2020

Case: An old friend

27 year old woman with AML

Myeloablative conditioning with Cytoxan / TBI

Double cord transplant

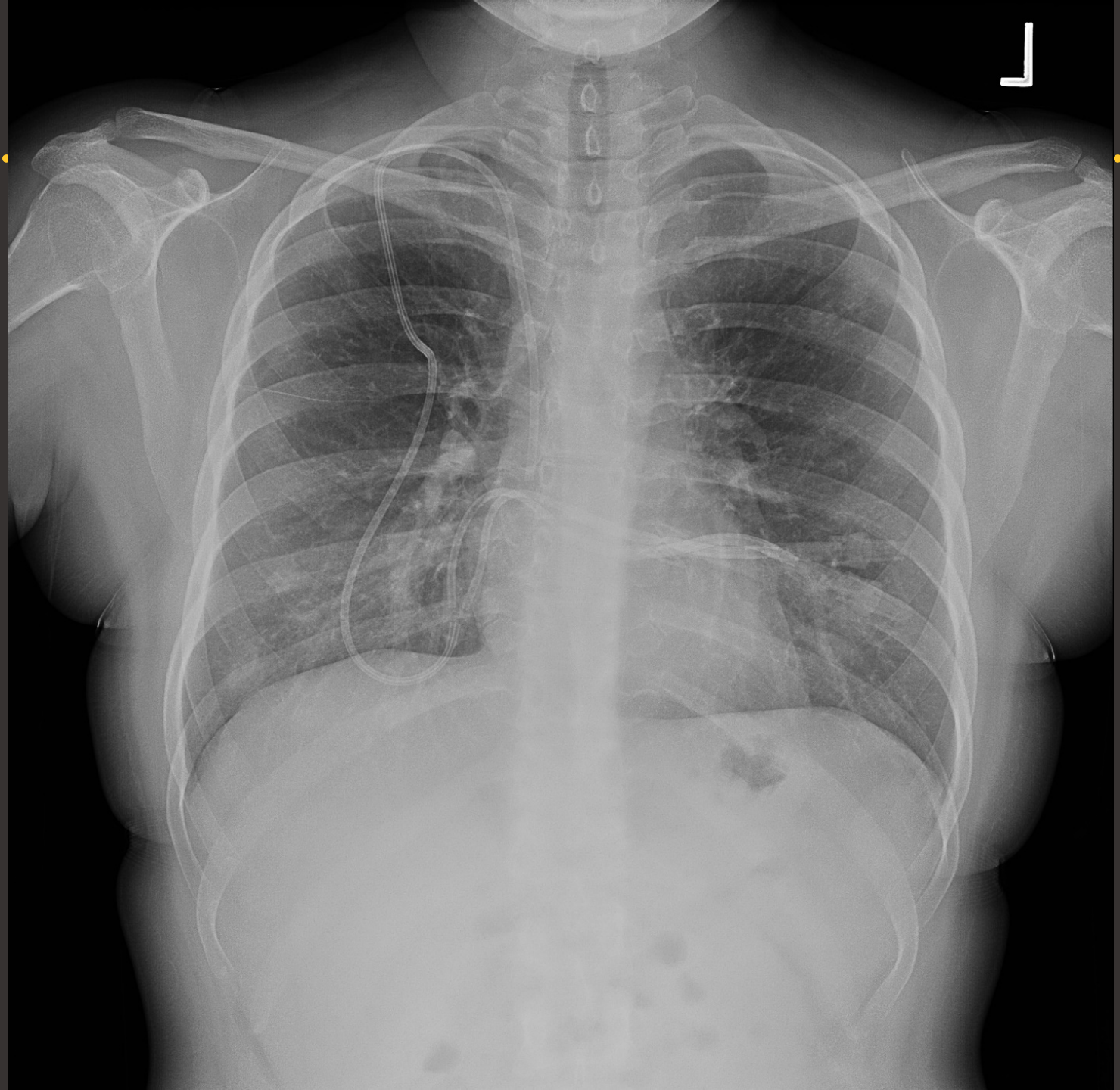
Acute GI GVHD requiring 1 mg/kg of steroids

Low level CMV re-activation

Discharged home

Day +24 developed abdominal pain, seen in clinic, CT abdomen negative

Day +25 fevers, admitted hypoxic to 88% on room air



Case: Continued

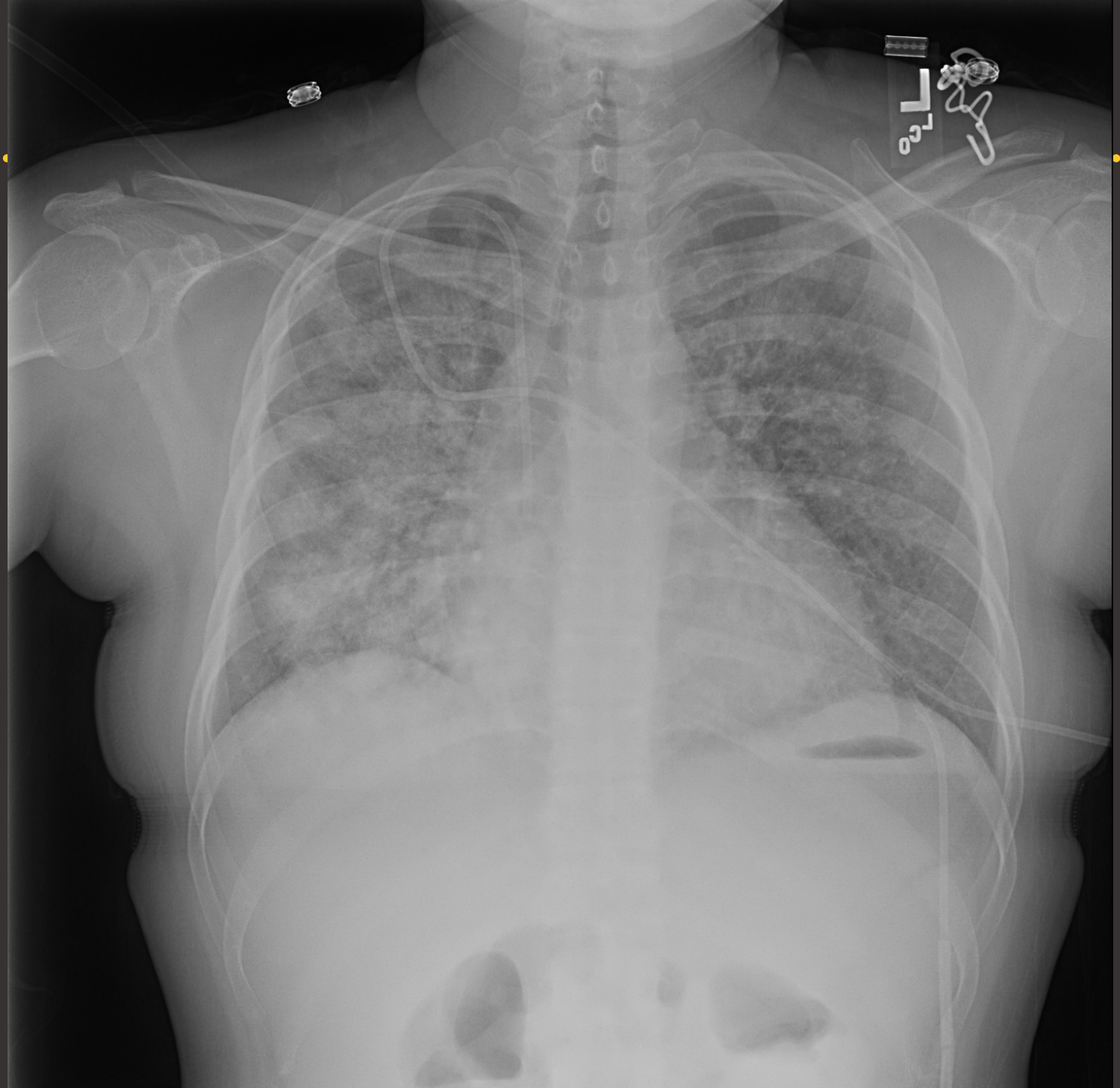
Empiric ceftazidime and vancomycin started

Worsened abdominal pain and hypoxia

Moved to ICU on non-breather mask

Ceftazidime broadened to ganciclovir

Repeat CXR



Cytomegalovirus

JCI The Journal of Clinical Investigation

CMV viral load kinetics as surrogate endpoints after allogeneic transplantation

Duke 2021

- Ubiquitous herpes virus, latent infections can reactivate

- Major risk determinant in allo-transplants: *What is the antibody status of the recipient?*
  - Seropositive recipients at highest risk

- Invasive disease is generally correlated with viremia
  - However, *remember GI disease can present without viremia*
  - PCR more sensitive and preferred over pp65 antigen assay

- Invasive disease can be reduced with pre-emptive therapy or prophylaxis

CMV *disease* is the clinical manifestation of CMV infection

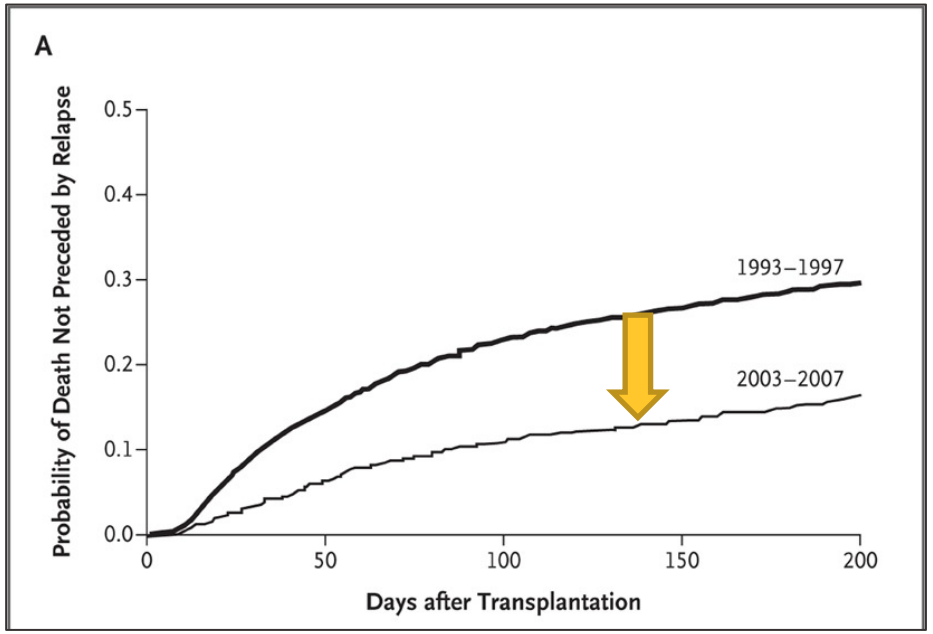
CMV Disease

CMV Viral Syndrome

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

Tissue Invasive Disease

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



Gooley, NEJM, 2010

CMV prevention strategies

Pre-emptive therapy

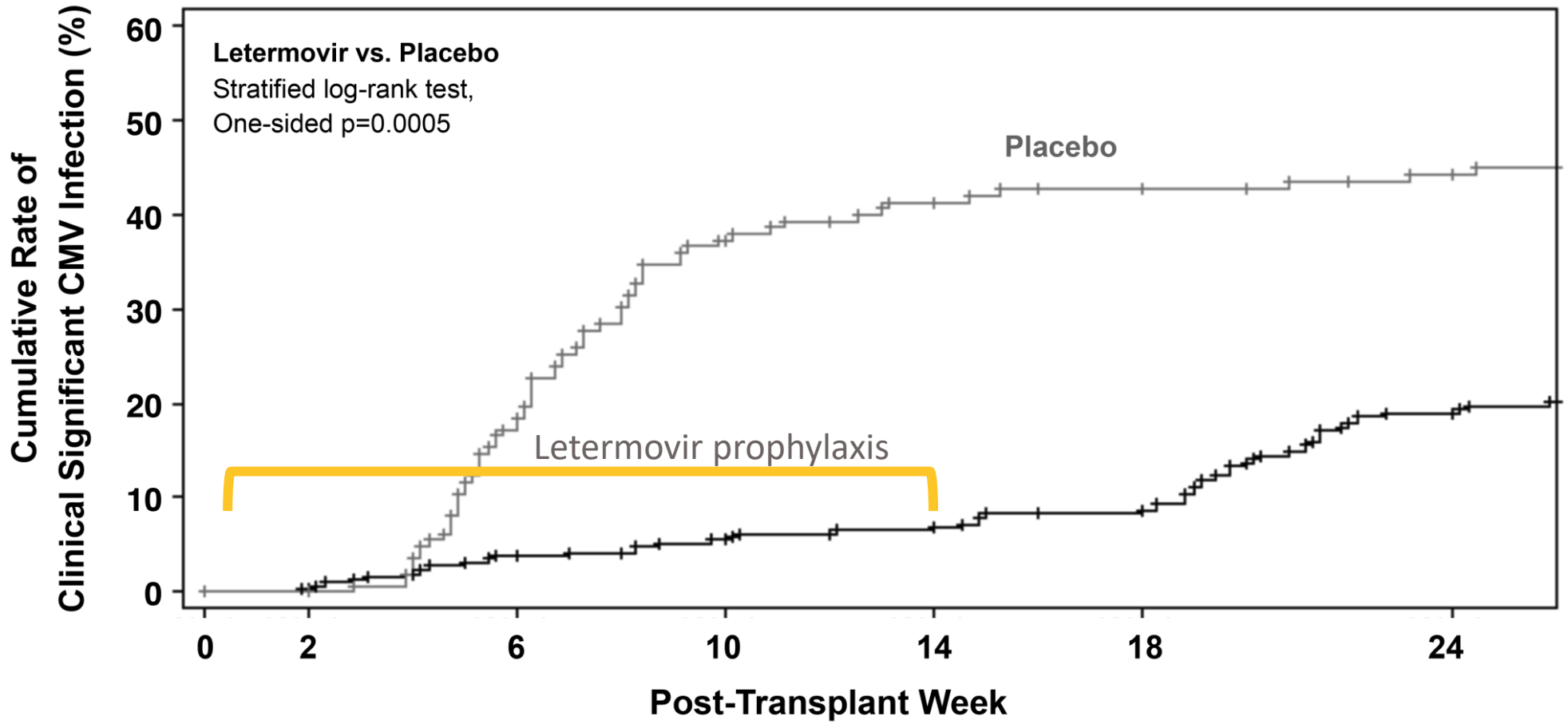
- Weekly surveillance with blood PCR to at least to day +100 in allogeneic transplant (longer if on high dose steroids)
- Early treatment with val(ganciclovir) or foscarnet

Prophylaxis

- (Val)ganciclovir – effective but bone marrow suppressive and generally avoided early post-transplant
- High dose val(acyclovir) – not marrow suppressive but less effective
- Letermovir – PO or IV formulation / no marrow suppression / increases levels of cyclosporine, sirolimus, and tacrolimus / decreases levels of voriconazole / low barrier of resistance / not active against HSV or VZV

Figure 1. Time to Onset of Clinically Significant CMV Infection

Subjects with undetectable CMV DNA at Randomization

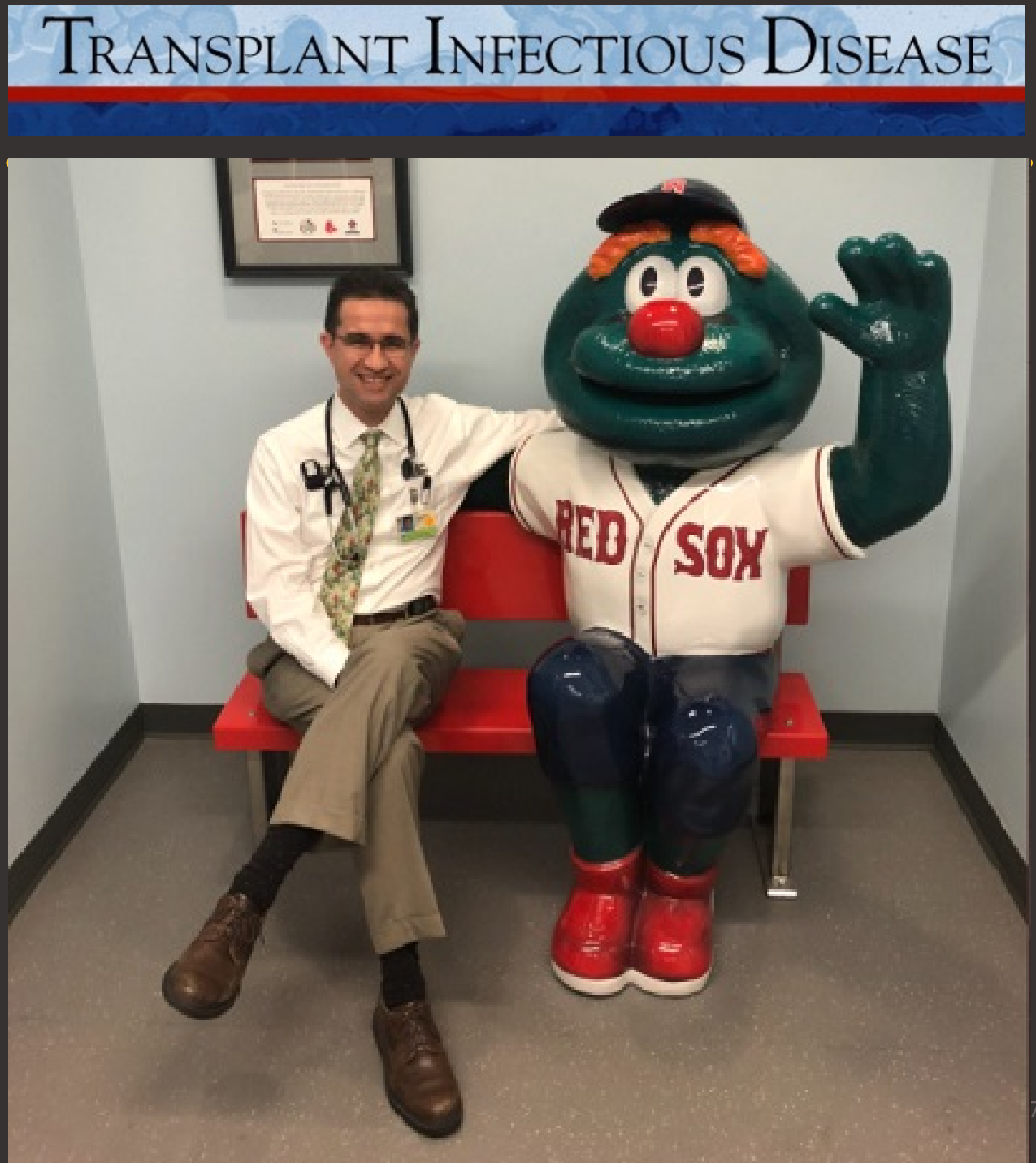


Letermovir	325	320	299	279	270	254	212
Placebo	170	169	135	96	85	77	70

Subjects at risk

Marty, NEJM, 2017

"Transplant Infectious Disease is saddened to announce the death of Editor-in-Chief Francisco Marty on April 8, 2021 from an unexpected and tragic accident. Francisco specialized in treating transplant and cancer patients, and was a dedicated clinician, patient advocate, and teacher, taking extraordinary joy in mentoring new generations of clinicians."



Treatment of CMV disease

- (Val)ganciclovir – effective / marrow suppressive / avoid PO formulation with GI disease
- Foscarnet – used with resistance / not marrow suppressive / nephrotoxic
- Cidofovir – used with resistance / nephrotoxic
- Letermovir – no clinical trials in HCT as treatment / theoretic concern for resistance as monotherapy
- Maribavir – phase 2 trial showed efficacy as pre-emptive therapy / phase 2 trial ongoing for resistant or refractory CMV post-transplant / not myelosuppressive
- CMV-specific T cells – phase 2/3 clinical trials ongoing

Abraham 2019

Case: Think of the children

Non-Hodgkin's lymphoma

Auto-transplant in December, now day +45

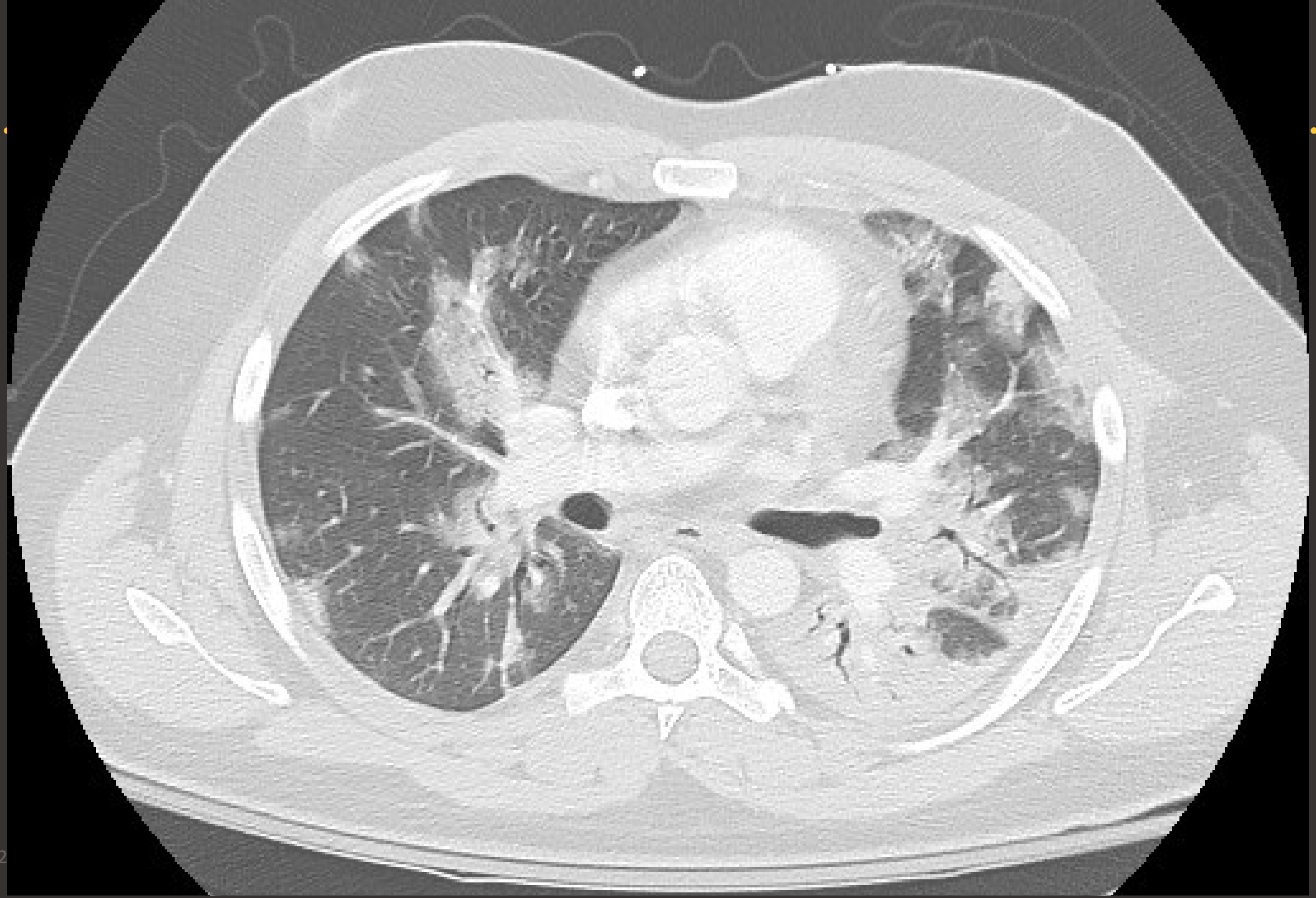
Neutrophils recovered and discharged home

Small children at home

Fever, myalgias, sore throat three days prior to admission

Develops shortness of breath and presents to the ED hypoxic with O2 sat 87%

Acutely decompensates and transferred to ICU



Case: Continued

BAL and nasal swabs positive for influenza

Treated with high dose oseltamivir

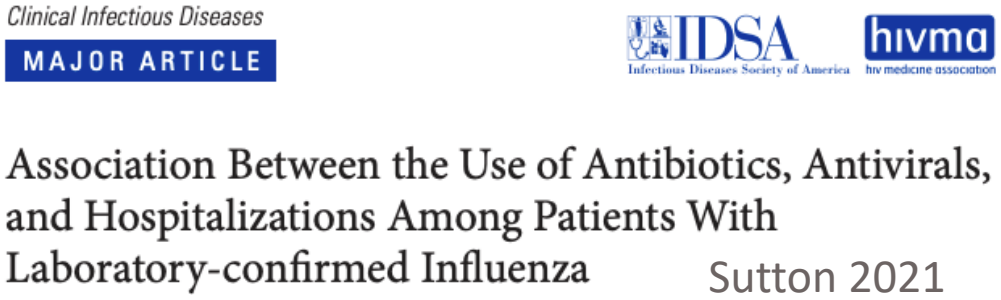
Intubated and proned in the ICU

Peramavir IV administered through compassionate use

In ICU for 4 weeks with ARDS

Rehab for 4 more weeks

Recovered and discharged home



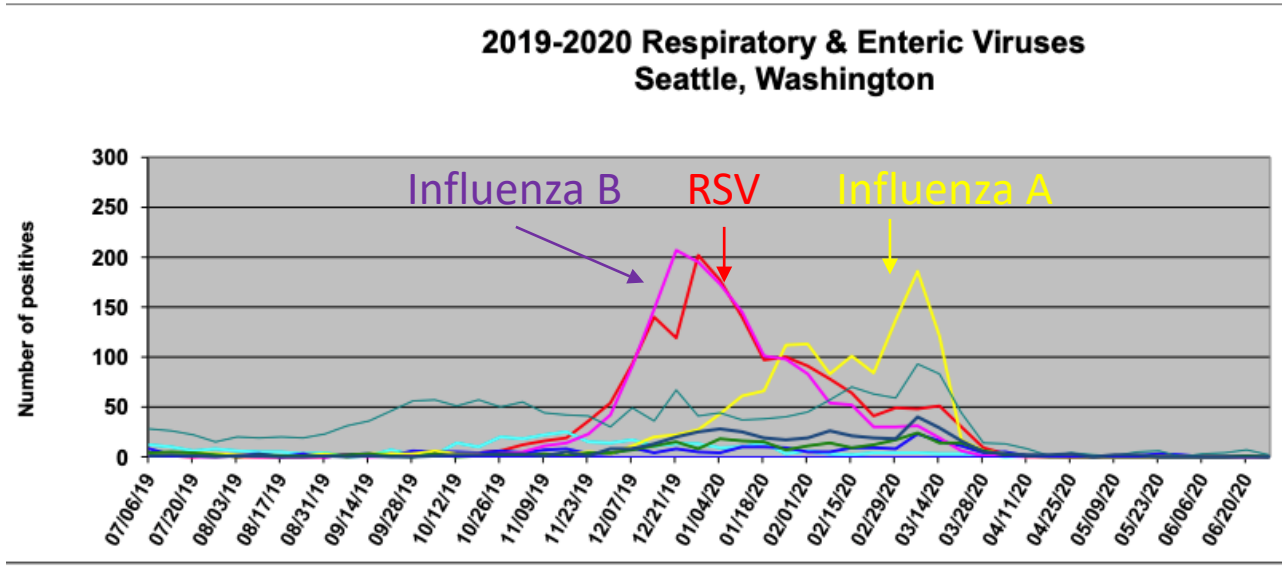
Prevention and early detection/treatment are critical

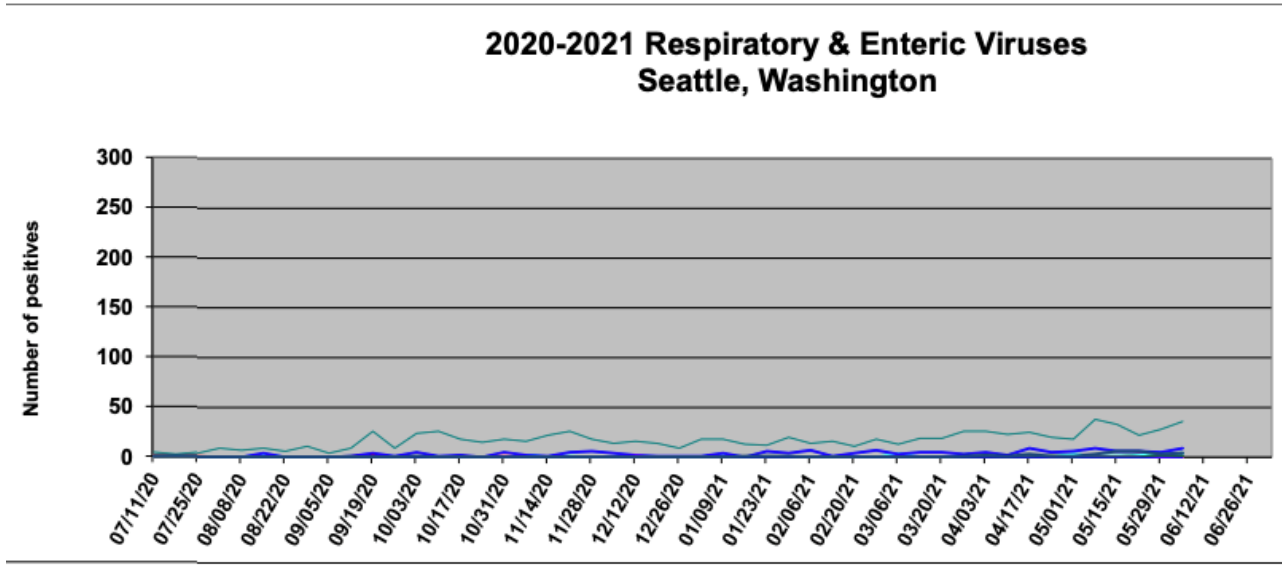
Baloxavir (single PO dose) or oseltamivir as *early treatment* for mild cases or *post-exposure prophylaxis* could prevent hospitalization


Cost of a Transplant: ~ $750,000

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

Influenza in the era of COVID-19

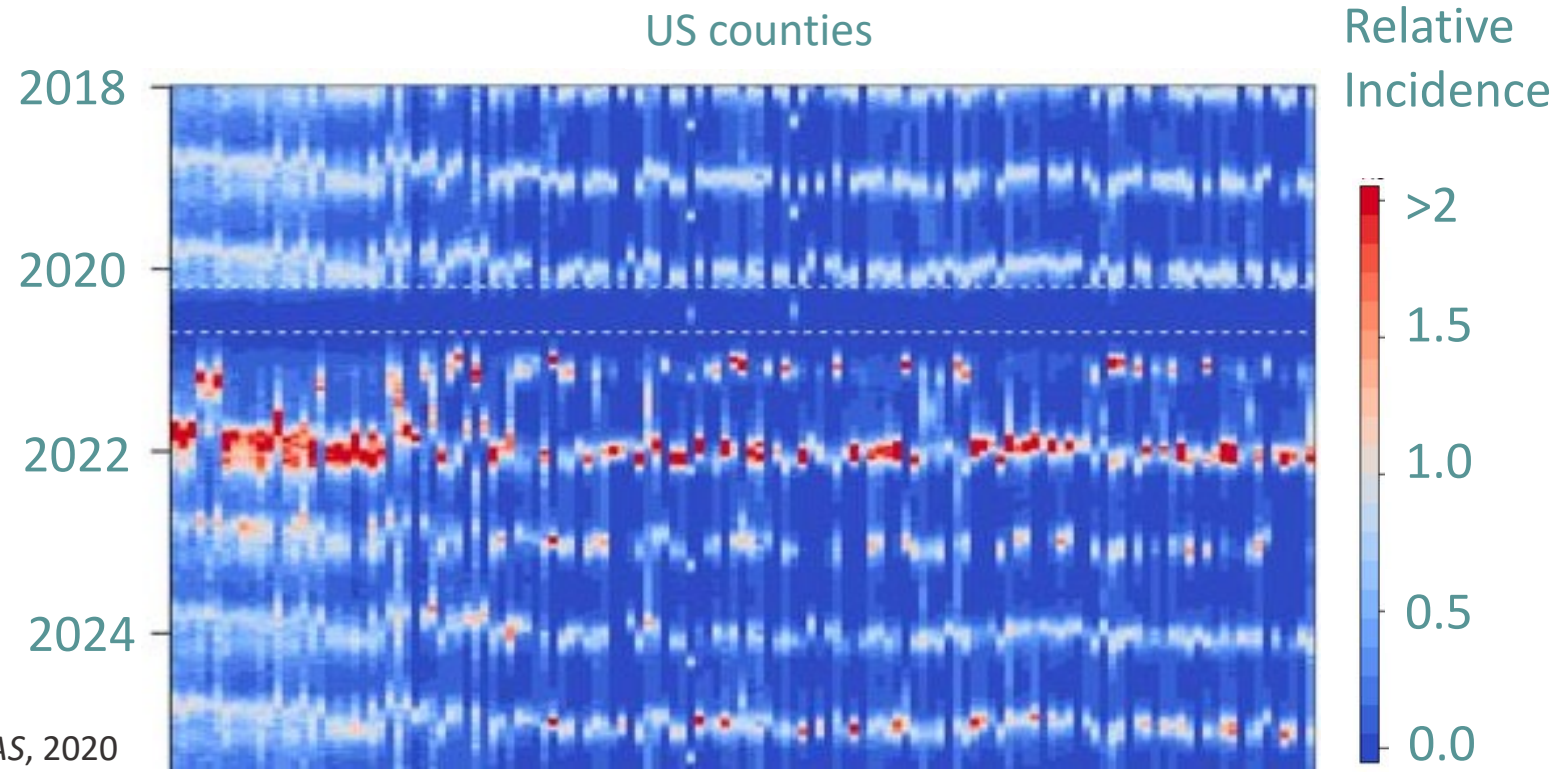




Source: UW Virology

The future of influenza?

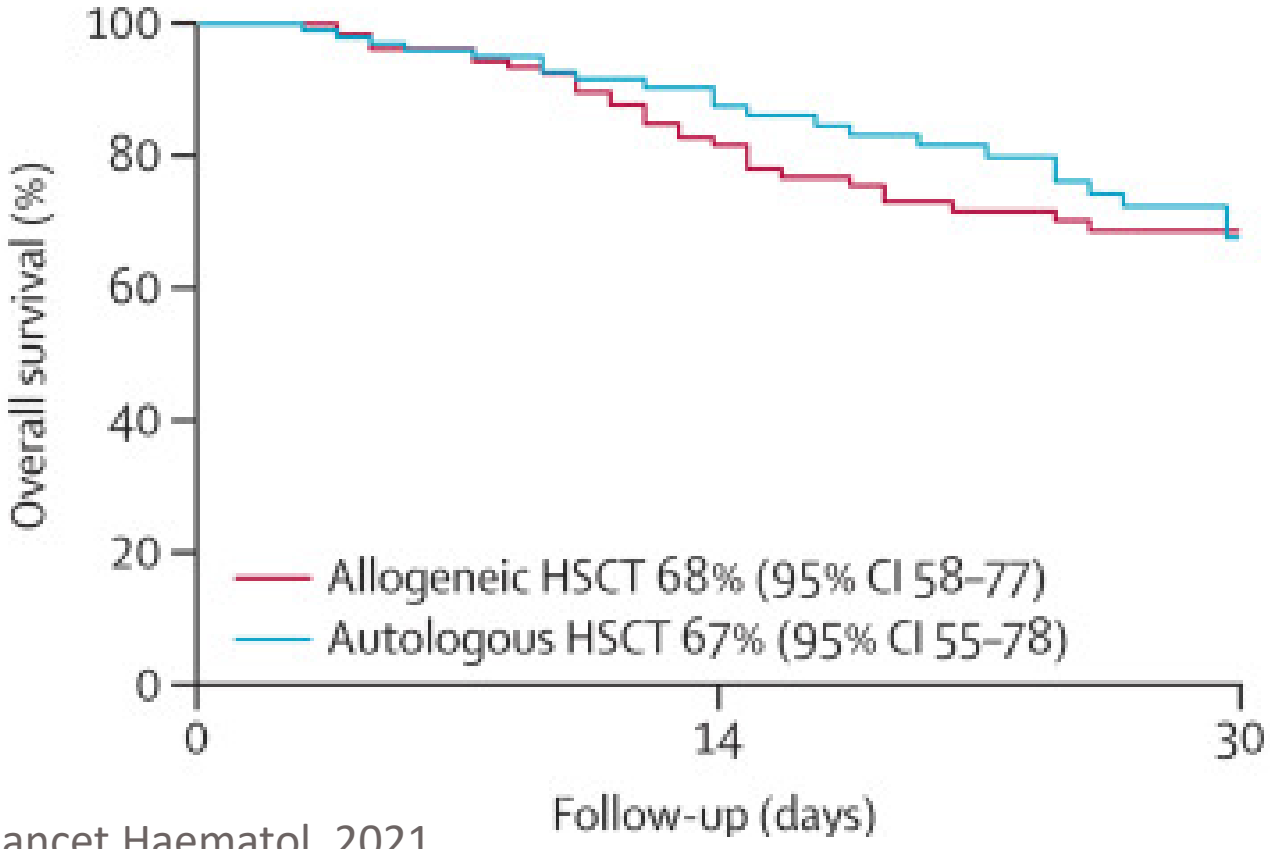
- Masking and social distancing have reduced the incidence of other respiratory viral infections
- The susceptible population to infection has increased
- Influenza vaccine efficacy likely will be low in the coming season due to lack of cases for strain prediction
- Models project large future outbreaks



Baker et al, *PNAS*, 2020

COVID-19 and transplant

- Poor survival in both autologous and allogeneic transplant recipients (30-day survival of 68%)
- Higher mortality if infection within 12 months of transplant, underlying lymphoma, age >50, male sex



Sharma, Lancet Haematol, 2021

COVID-19 and the immunocompromised

Prolonged shedding (months) of live virus in cancer patients has been reported

Vaccination

- Antibody responses blunted in hematologic malignancies or with B cell targeted therapies
- No formal guidance on checking antibody titers
- Still recommended in cancer patients (something better than nothing)
- Checkpoint inhibitors are not a contraindication to vaccination
- Wait at least 3 months post-transplant or CAR T-cell therapy to vaccinate against COVID-19

Treatment (data mostly extrapolated from non-immunocompromised studies)

- Outpatient
  - Monoclonal antibodies and convalescent plasma – reduces progression to severe disease
- Inpatient
  - Dexamethasone – reduces mortality among hospitalized patients
  - Tocilizumab – combination with dexamethasone, reduces mortality
  - Remdesivir – reduces time to recovery
  - Baricitinib – combination with remdesivir further reduces time to recovery

Aydillo, NEJM, 2020
Herishanu, Blood, 2021
Libster, NEJM, 2021

Concluding remarks

Vigilance needed with new drugs used in cancer patients

- Ibrutinib – invasive fungal infections (even in the absence of neutropenia)
- Idelalisib – Pneumocystis
- Eculizumab – meningococcus
- Brentuximab – Pneumocystis, CMV, HBV reactivation, JC virus-associated PML
- Ruxolitinib – HBV (and possibly TB) reactivation

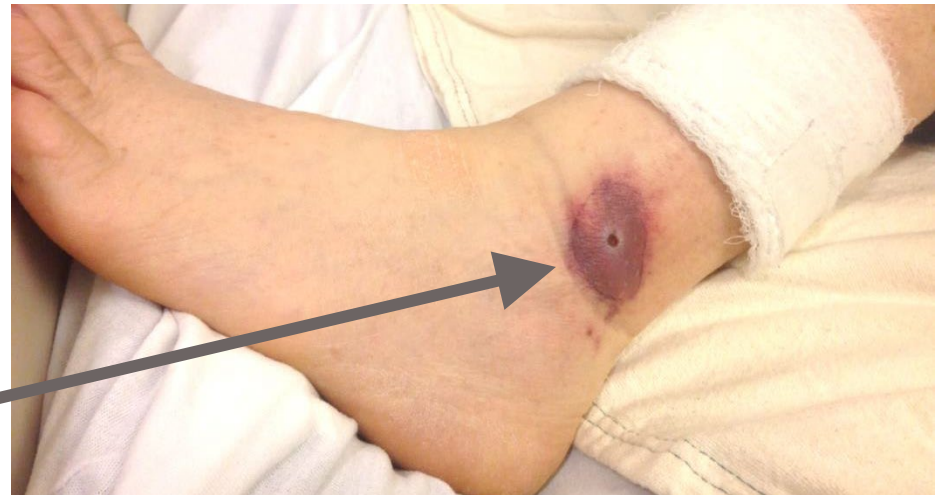
Maschmeyer, Leukemia, 2019

Constant vigilance, but don't forget about non-infectious mimics

- Drug toxicity
- Drug allergy
- Drug fever
- Underlying malignancy
- Sweet's syndrome
- Pulmonary embolism
- Alveolar hemorrhage
- Transfusion reactions
- COP/BOOP/IPS
- GHVD/Rejection

Sweet's syndrome

Disseminated Aspergillus



Summary

1. Infections in cancer and HCT recipients can be understood through a framework of location and timing
2. Prophylactic antibiotics/antivirals/antifungals have dramatically improved survival
3. Every minute counts with antibiotics for neutropenic fever
4. Novel drugs used in cancer are associated with infectious risks
5. Thankfully, we also have novel antimicrobials in the pipeline
6. COVID-19 has changed the respiratory virus landscape but be prepared
7. Don’t count out the oldies (influenza, RSV) quite yet

Questions

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