

Common Infectious Disease
Conundrums in Cancer

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Conflicts of interest

- None

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Objectives

- Workup and management of febrile neutropenia
- Workup and management of pulmonary nodules

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Case #1

- Ms. JM: 68 Y F with follicular lymphoma, presenting with fevers to 38.6°C, 2 weeks after R-CHOP
- ROS: rhinorrhea, a scratchy throat, an occasional non-productive cough, and watery diarrhea (3-4x in a day)
- No headaches, shortness of breath, abdominal pain, **no dysuria**, or rashes

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Case #1

- On examination, her vitals: Temp 38.3°C, HR 97, BP 125/69, 96% on RA.
 - Mild erythema in posterior oropharynx
 - Lung sounds are clear
 - Abdomen is soft and non-tender
 - No rashes
- Her labs are notable for:
 - WBC of 1300 cells/mL with an ANC of 900 cells/mL
 - Hgb 9.1, and platelets of 115K/dL
 - Cr 0.8 mg/dL

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Original Article | Published: 27 September 2019
Urine cultures at the onset of febrile neutropenia rarely impact antibiotic management in asymptomatic adult cancer patients
 Sam E. Girgis, Patrick Datta, Zoe Loh, Orta Estacio, Douglas E. Johnson, Eliza A. Heekes & Andrew Girgis
 Supportive Care in Cancer 27, 1223–1227 (2019) | [View this article](#)
 284 Accesses | 2 Citations | Metrics

- Retrospective review: 433 episodes of FN in 317 patients with hematologic malignancies (2011-2015)
- Positive urine cultures (RR = 7.4, $p < 0.0001$)
 - Symptomatic (n=48): 19%
 - Asymptomatic: 2.5%
- Change in antibiotic management (RR = 9.8, $p = 0.01$)
 - Symptomatic: 6.3%
 - Asymptomatic: 0.6%

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What do the guidelines say?

- IDSA Asymptomatic bacteriuria guidelines (CID, 2019)
 - "Patients with low-risk neutropenia (ANC <100 cells/ mm³ for ≤7 days, clinically stable) have only a very small risk of infection, and there is no evidence to suggest that asymptomatic bacteriuria has greater risk than for non-neutropenic populations"
 - "In patients with high-risk neutropenia...we make no recommendation for screening"
 - Screening and treatment of asymptomatic bacteriuria only in **pregnant women** or individuals **prior to undergoing invasive urologic procedures**
 - Unclear: urologic malignancies, stents, chronic catheters

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Initial risk assessment: IDSA FN 2010

- Low risk → oral antibiotics
 - Limited duration of severe neutropenia (ANC < 100 cells/mL for <7d, clinically stable)
 - MASCC risk score ≥ 21

The Multinational Association for Supportive Care in Cancer Risk-Index Score	
Characteristic	Weight
Burden of febrile neutropenia with no or mild symptoms ^a	5
No hypotension (systolic blood pressure >90 mmHg)	5
No chronic obstructive pulmonary disease ^b	4
Solid tumor or hematologic malignancy with no previous fungal infection ^c	4
No dehydration requiring parenteral fluids	3
Burden of febrile neutropenia with moderate symptoms ^a	3
Outpatient status	3
Age <80 years	2

Freifeld AG et al. CID, 2010

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High-risk febrile neutropenia

- BMT
- Anticipated severe neutropenia (ANC <100 cells/uL, >7 days)
- Severe comorbidities: COPD, heart disease, renal dysfunction
- Mucositis grade 3-4
- MASCC <21

Freifeld AG et al. CID, 2010

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Workup of febrile neutropenia

- Infectious workup: includes a detailed history and physical exam



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Infectious workup by system: a few highlights

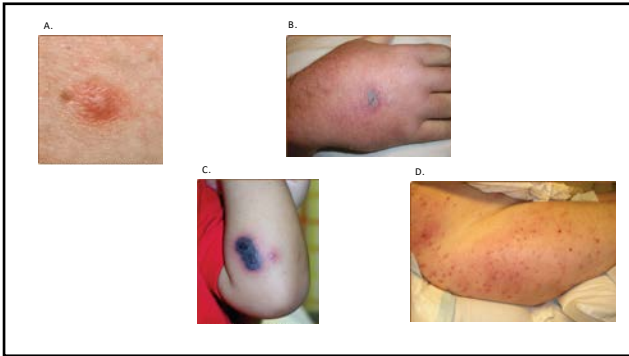
- Oral lesions
 - Vesicular → HSV/VZV, rarely CMV (swab and empiric treatment)
 - Ulcerated → HSV/VZV, rarely CMV, Histoplasma, TB
 - Necrotic → Molds
 - Dental pain/abscesses → Anaerobic bacteria
- Sinus congestion and pain
 - Unilateral sinus congestion or pain → Strep, Staph, Pseudomonas and other gram-negative bacteria, rarely molds (CT sinus/orbit, ENT eval)
 - Bilateral sinus congestion → Respiratory pathogen panel

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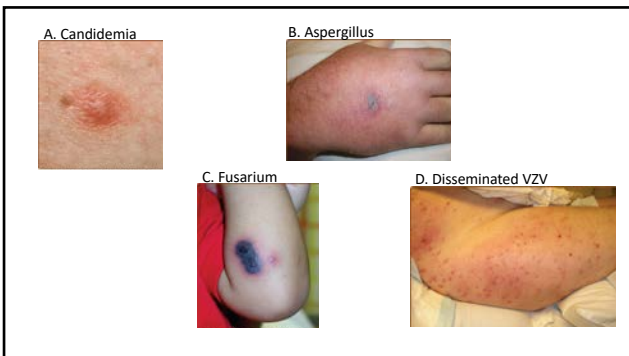
Infectious workup by system

- Diarrhea (3 or more watery stools in 24h)
 - Watery → *C.diff*, Norovirus
 - Bloody → Salmonella, Campylobacter, E.coli (GI PCR panel)
 - CMV in very immunocompromised (BMT)
- Skin
 - Pustular → Candidemia, Strep or Staph folliculitis
 - Purpuric or necrotic → ecthyma gangrenosum (molds, Pseudomonas and other gram-negative organisms, Staph aureus)
 - Nodular → molds, endemic fungi, Mycobacteria (TB and non-TB), Nocardia
 - Vesicular or ulcerated → HSV, VZV
- Lines → date of placement and appearance

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Consider non-infectious causes of febrile neutropenia

- Malignancy
- Cytokine release syndrome or engraftment syndrome
- DVT/PE
- Drug fever (especially beta-lactam antibiotics)
 - Look for eosinophilia and /or transaminitis
- Aspiration
- Acalculous cholecystitis
- Pancreatitis
- Mesenteric ischemia
- Adrenal insufficiency
- Thyrotoxicosis

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High-risk febrile neutropenia management

- Empiric therapy
 - Cefepime
 - Ceftazidime (minimal *Strep* coverage, possible *Strep* breakthrough)
 - Piperacillin-tazobactam
 - Meropenem

→ No distinctions made between antibiotics (IDSA FN guidelines 2010)

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Why our antibiotic choices matter: our microbiome!



https://medium.com/@Routy/the-development-of-the-gut-microbiome-1082a2a4171c

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Immune checkpoint inhibitor therapy and the gut microbiome

Patients	Therapy	Observations in Responders	Reference
Advanced-stage cancers (NSCLC, RCC, urothelial CA) n=249	Anti-PD-1 or Anti-PD-L1	<ul style="list-style-type: none"> • Antibiotics before treatment linked to shorter PFS • <i>Akkermansia muciniphila</i> enriched in responders 	Routy Science, 2018
Metastatic melanoma n=43	Anti-PD-1	<ul style="list-style-type: none"> • <i>Faecalibacterium</i> linked with: <ul style="list-style-type: none"> • Longer PFS at 6 months • Increased density of CD8+ T-cells in tumor microenvironment 	Gopalakrishnan Science, 2018
Metastatic melanoma n=42	Anti-PD-1 or Anti-CTLA-4	<ul style="list-style-type: none"> • Responders enriched in <i>Bifidobacterium longum</i>, <i>Collinsella aerofaciens</i>, and <i>Enterococcus faecium</i> • <i>Akkermansia muciniphila</i> present only in responders 	Mattson Science, 2018
Metastatic melanoma n=65	Anti-PD-1 or Anti-CTLA-4	<ul style="list-style-type: none"> • <i>Faecalibacterium</i>, Firmicutes, and <i>Dorea formicigenerans</i> linked with longer PFS 	Chaput Ann. Oncol., 2017
Metastatic melanoma n=39	Anti-PD-1 and/or Anti-CTLA-4	<ul style="list-style-type: none"> • Responders to all therapies enriched for <i>Bacteroides caccae</i> • Responders to Anti-CTLA-4 enriched in <i>Faecalibacterium prausnitzii</i>, <i>Bacteroides thetaiotaomicron</i>, <i>Holdemanella filiformis</i> 	Frankel Neoplasia, 2017

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Save the anaerobes!



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Aerobic v. **anaerobic** antibacterial activity

- Cefepime → less anaerobic activity
- Ceftazidime → less anaerobic activity
- Piperacillin-tazobactam → more anaerobic activity
- Meropenem → more anaerobic activity

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What about empiric IV Vancomycin?

1. Hemodynamic instability
2. Pneumonia
3. Clinically apparent IV catheter infection
4. Known colonization with resistant Strep or Staph
5. Skin and soft-tissue infection
6. Severe mucositis if Ceftazidime is used

→ STOP Vanc if no evidence for MRSA after 2-3 days

Freifeld AG et al. CID, 2010

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What to do when patients remain febrile on antibiotics?

- If <4-7 days and hemodynamically stable → Continue on current therapy
- If >4-7 days and hemodynamically stable → Repeat workup, get a CT chest +/- CT sinus, **add mold coverage**
- If hemodynamically unstable → Repeat workup, imaging, and consider adding antimicrobial coverage (*MRSA, Candida*, multidrug-resistant organisms)

Freifeld AG et al. CID, 2010

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When to stop or narrow antibiotics?

- Standard: Afebrile and ANC>500 cells/uL
 - Or continue as clinical diagnosis warrants
- Early de-escalation
 - At UNC (BMT): If afebrile for 5 days but still neutropenic in the absence of documented infection, de-escalate and restart prophylaxis

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Early de-escalation is safe and decreases time on IV antibiotics

- Randomization: early de-escalation vs. standard (n=157)
 - Inclusion: High-risk adults (heme malignancy and BMT) after 72h, afebrile without diagnosis

	Experimental group (n=78)	Control group (n=79)	Between-group absolute difference (95% CI)	p value
Source of fever				
Unknown	31 (40%)	32 (41%)	0.8% (-14.6 to 16.1)	0.92
Oral mucositis	14 (18%)	17 (22%)	3.5% (-0.9 to 16.0)	0.57
Abdominal	10 (13%)	10 (13%)	0.3% (-12.3 to 12.6)	0.97
Pulmonary	7 (9%)	2 (3%)	6.4% (-0.8 to 13.2)	0.10
Perianal	2 (3%)	5 (6%)	3.7% (-2.7 to 10.2)	0.44
Other	11 (14%)	6 (8%)	6.5% (-3.2 to 16.2)	0.19
Median neutropenia duration, days	14 (9.5-24.0)	11 (8.4-21.3)	-4.1 (-6.1 to -1.0)	0.13
Neutropenia at EAT withdrawal	43 (55%)	8 (10%)	45.5% (28 to 57)	<0.0001
Recurrent fever (at least one episode)	11 (14%)	14 (18%)	3.6% (-7.8 to 15.1)	0.58
Infections per 1000 patient days* (N)	16.8 (9)	16.4 (10)	0.4 (-7.3 to 6.1)	0.17
Bacteremia	4 (7)	6 (4)	2.5 (-1.0 to 6.0)	0.20
Invasive fungal infection	3 (5)	4 (7)	2.8 (-0.4 to 6.2)	0.12
Adverse events per 1000 patient days** (N)	15.9 (34)	13.8 (29)	20.7 (-6.6 to 47)	0.057
Serious adverse events per 1000 patient days** (N)	5.1 (11)	12.7 (27)	7.6 (-1.9 to 13.2)	0.0087

Aguilar-Guisado et al. Lancet Hematology, 2017

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Tips for when you find an infection

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Bloodstream infection management tip #1

- When to take the line out*?
 - “Long-term catheters should be removed from patients with CRBSI associated with any of the following conditions:
 1. Severe sepsis
 2. Suppurative thrombophlebitis
 3. Endocarditis
 4. Continued bacteremia despite 72 h of adequate antimicrobial therapy
 5. Infections due to *S. aureus*, *P. aeruginosa*, *fungi*, or *mycobacteria*”

→ “Sticky” bad bugs = take the line out



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Bloodstream infection management tip #2

- Consult ID for any bloodstream infections
- Especially: *Staph aureus*, *Candida/molds*, *Pseudomonas aeruginosa*, and multidrug-resistant organisms
 - ID consult = reduced mortality and better outcomes

Chesdachai S, et al. OFID, 2020

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C.difficile management tips: IDSA 2021 update!

- First *C.diff* occurrence: Fidaxomicin > PO Vancomycin
- *C.diff* recurrence: Fidaxomicin > PO Vancomycin taper
- Multiple *C.diff* recurrences: Fidaxomicin > PO Vancomycin taper
 - Alternatives: PO Vanc + Rifaximin, fecal microbiota transplant (FMT)

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Fidaxomicin use at UNC

→ Recurrent disease
OR
→ Any 2 of the following

- Age > 65 years old
- Severe *C.diff* infection (WBC >15K, or Cr <1.5)
- Immunocompromised state (malignancy, immunosuppression, SOT/BMT)
- Receiving antibiotics for infection (not *C.diff*)

OR
→ ID/GI/Antimicrobial stewardship consult

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Summary of teaching points from case #1

1. Urine cultures only if symptomatic
2. Oral antibiotic management of low-risk patients with febrile neutropenia (e.g. Cipro + Augmentin)
3. Clues to look for in assessment of patients with febrile neutropenia (e.g. thorough skin exam)
4. Not all IV antibiotics are created equal (avoid anaerobically-active antibiotics)
5. Consider early de-escalation of antibiotics if afebrile and without infection x 5 days (instead of waiting for ANC >500)
6. Take out the line with severe bloodstream infections and infections with specific "sticky" organisms (*Staph aureus*, *Candida*, *Pseudomonas*)
7. Fidaxomicin is now first-line treatment for initial *C.diff* infection

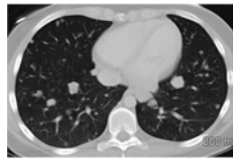
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Case #2

- A 34-year-old man with AML underwent allogeneic hemopoietic stem cell transplantation
- He became febrile to 39°C starting on day +7, ANC 0. He was started on cefepime and pan-cultured yet all his studies remained negative
- After 4 days of fevers, the patient remains hemodynamically stable

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Case #2 continued



- His CT chest is shown
- Differential diagnosis?
 - Fungal: *Aspergillus*, *Mucorales*, endemic fungi (*Crypto*, *Histo*, *Blasto*, *Cocci*)
 - Bacterial: *Nocardia*, *TB* or other *Mycobacteria*, *Actinomyces*
 - (Less likely viral or parasitic)
 - Non-infectious: drug-reaction, malignancy

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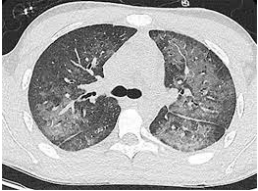
The Andermann workup™ for nodular pulmonary lesions

- 1. Assess exposure history**
 - a. TB: prison, foreign travel to endemic areas, homeless, exposure to known case at any point in history
 - b. Animal exposure: Birds (*Crypto*), bats/caves (*Histo*), horses (*Rhodococcus equi*)
 - c. Hobbies/work: gardening (*Nocardia*), construction (high fungal exposure)
 - d. Travel: West Coast/Arizona (*Coccidioides*), Latin America (*Paracoccidioides*), SE Asia (*Penicillium*)
 - e. Other: Recent dental procedures/dental disease (*Actinomyces*)
- 2. Serum/urine workup**
 - a. Urine: *Histo* urine Ag
 - b. Serum: *Crypto* Ag, *Histo* Ag, fungal antibody panel, fungitell, galactomannan, +/- Quantiferon
- 3. BAL with biopsy (ideally before starting antifungals)**
 - a. Stains and cultures: Bacterial, fungal, AFB
 - b. Galactomannan
 - c. +/- *Actinomyces* screen
 - d. Less likely to request PJP DFA, CMV or other viruses

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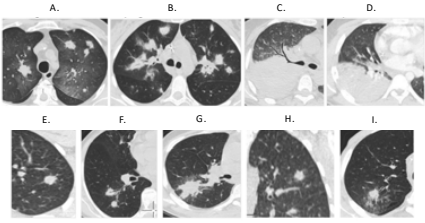
Differential diagnosis for diffuse ground glass on CT chest

- Viruses (respiratory viruses, herpes viruses)
- *Pneumocystis jiroveci*
- *Toxoplasma gondii*
- Atypical bacteria
- Drug toxicity
- Volume overload



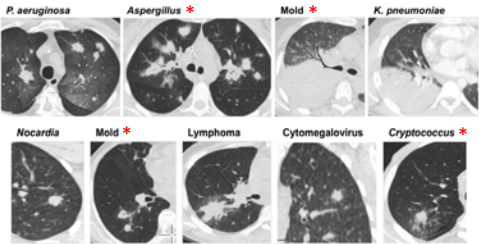
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Find the fungus!



Lionakis MS et al, CID, 2018

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Lionakis MS et al, CID, 2018

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ASTCT 2021 guidelines for Aspergillus infection

Event		Recommendation
Treatment	First-line	Voriconazole
	Alternative	Isavuconazole, Posaconazole, or Ambisome (azoles first-line in CNS)
Failure on azole		<ul style="list-style-type: none"> • Ambisome 5mg/kg/day • Resistance testing
Duration		Radiographic resolution or at least 12 weeks, whichever is later

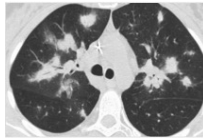
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Case #2 continued

You start him on voriconazole and 2 weeks later his ANC is higher at 500. His chest CT looks worse—the lesions are bigger. He reports that he is compliant with his medication.

Why do you think the lesions became larger?

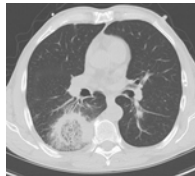
1. **Failure**
 - a. Wrong bug: Mucorales are resistant to vori
 - b. Wrong drug: Azole-resistant Aspergillus
 - c. Wrong dose: Vori trough <2
 - d. Wrong host: Immune response inadequate
2. **Not failure**
 - a. Neutrophils are engrafting leading to pulmonary inflammation



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What if he were to have the following CT chest finding?

- **Reverse halo sign**
- Caused by rapid expansion, angioinvasion, and resulting loss of blood supply in central area of necrosis
- More commonly seen with Mucorales but also seen with other molds



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Treatment of Mucorales infection

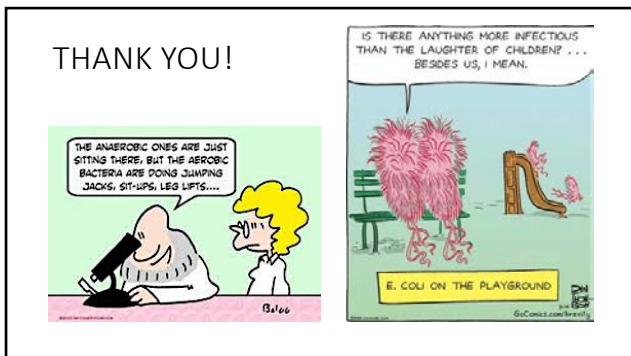
- No standard guidelines exist
- **Surgical resection is key feature of management**
- Ambisome is first-line
- **Delaying Ambisome therapy by more than 6 days increases mortality 2-fold** (Chamilos et al., CID, 2008)

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Summary of teaching points from case #2

1. CT chest if febrile neutropenia >4-7 days
2. If hemodynamically stable, no broadening antibiotic coverage
3. Consider a broad differential in your assessment and management of pulmonary nodules
4. First-line therapy for pulmonary Aspergillus remains Voriconazole but Isavuconazole and Posaconazole are options now as well
5. Treatment of an invasive pulmonary fungal infection that fails an azole is Ambisome (STAT!)
6. Consider surgical management of Mucorales infections (reverse halo!)

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