

Opportunistic Infections in Immunocompromised Patients

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The following person in control of this activity's content have relevant financial relationships:

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Learning Objectives

- Assess the advantages and disadvantages of pharmacotherapies for opportunistic infections in immunocompromised patients, including antimicrobial spectrum of activity, pharmacokinetics, and pharmacodynamics.
- Select the most appropriate pharmacotherapeutic plan and monitoring based on patient- and disease-specific information and best available evidence.
- Interpret signs, symptoms, and laboratory and other relevant diagnostic test results.
- Recommend modifications of patient-specific treatment plans based on efficacy, immunologic response, and adverse effects.
- Identify preventative therapies in immunocompromised patients.

Opportunistic Infections in Immunocompromised Patients: Bacterial Infections and Fungal Prophylaxis

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Patient Case

- NV is a 36-year-old woman
- Admitted to the hospital for a matched unrelated donor allogeneic hematopoietic stem cell transplant (HCT) with busulfan/fludarabine/anti-thymocyte globulin (ATG) conditioning (currently transplant day -5)
- Screening serologies indicate NV has had a past infection with cytomegalovirus (CMV, IgG+ and IgM-) with a seronegative donor
- She currently has no complaints or symptoms and is eager to receive her transplant

Patient Case

- PMH:
 - Acute myeloid leukemia (AML), in second complete remission
 - Initially diagnosed 2 years previously with remission lasting 7 months following standard 7+3 induction (idarubicin and cytarabine), reinduced with salvage FLAG (fludarabine, idarubicin, cytarabine) and now undergoing allogeneic HCT
 - No significant past medical history
 - Multiple episodes of febrile neutropenia during induction / reinduction chemotherapy, no documented infections or known colonization

Patient Case

- Current Medications:
 - Busulfan (pharmacokinetic dosing to area-under-the-curve of 5000 $\mu\text{mol}/\text{min}$), IV days -6 to -3
 - Fludarabine 40 mg/m² IV days -6 to -3
 - ATG 0.5 mg/kg IV day -3 and ATG 2 mg/kg IV day -2
 - Phenytoin 600 mg orally daily (seizure prophylaxis), day -7 to day -3
 - Ondansetron 16 mg IV as needed for nausea prevention (premedication)
 - Methylprednisolone 100 mg IV as needed for prevention of infusion reaction (premedication)
 - Diphenhydramine 50 mg IV as needed for prevention of infusion reaction (premedication)
 - Famotidine 20 mg orally twice daily
 - Tacrolimus 0.5 mg/day IV continuous, starting day -2

Patient Case

- BP: 120/76 mmHg HR: 65 beats/min T: 37.4°C
RR: 14 breaths/min O₂ Sat: 99% room air
- Ht: 157cm Wt: 62.4kg
- Gen: Awake, appropriate mood and demeanor
- Physical: Notable only for the presence of a right brachial triple-lumen peripherally inserted central catheter (PICC)
- Pertinent labs:
 - WBC: 2.6×10^3 cells/mm³ (85% neutrophils, 12% lymphocytes)
 - SCr: 0.9 mg/dL
- QTc interval (from electrocardiogram 3 days ago): 378 msec

Question 1: Which of the following is the most appropriate antibiotic prophylaxis for NV during the neutropenic phase post-transplant?

- A. Amoxicillin-clavulanate
- B. Moxifloxacin
- C. Levofloxacin
- D. Cefdinir

Infectious Complications Following Hematopoietic Stem Cell Transplantation (HSCT)



Tomblyn M et al. *Biol Blood Marrow Transplant.* 2009; 15:1143-1238.

Immunosuppressive Effects of Common Medications

Medication	Effect
Corticosteroids	Lymphopenia (predominantly T-cell), impaired chemotaxis, others
Tacrolimus / cyclosporine	Depressed T-cell response
Mycophenolate	Lymphopenia, depressed B-cell response
Rituximab	B-cell apoptosis
Alemtuzumab	Profound lymphopenia
Antithymocyte globulin	Profound T-cell lymphopenia
Conventional chemotherapy	Significant leukopenia

- Immunosuppressive effects of medications are additive in sometimes unpredictable ways
- Immunosuppressive effects may last for months or years following administration

Prophylactic Antibiotics in Neutropenic Cancer Patients

- Infection risk increases with degree and duration of neutropenia
- Gram-positive infections (e.g., *Staphylococcus epidermidis*, oral streptococci) most common
- Gram-negative infections (e.g., *Pseudomonas aeruginosa*, *Escherichia coli*) most associated with morbidity and mortality
- Cochrane Database of Systematic Reviews
 - Antibiotic prophylaxis in afebrile neutropenic patients significantly reduces all-cause mortality
 - Prophylaxis recommended in patients with hematologic malignancy (fluoroquinolones preferred)

Gafer-Gvili A et al. *Cochrane Database Syst Rev*. 2008; 1:artCD004386.
Freifeld AG et al. *Clin Infect Dis*. 2011; 52:e56-93.

Recommended Antibiotic Prophylaxis in Cancer Patients

Organization	Antimicrobial prophylaxis recommendation
National Comprehensive Cancer Network® (NCCN®)	Consider fluoroquinolone prophylaxis in intermediate / high risk patients
Infectious Diseases Society of America (IDSA)	Consider fluoroquinolone prophylaxis for patients with anticipated prolonged, profound neutropenia (i.e., absolute neutrophil count [ANC] < 100 cells/mm ³ for > 7 days)
American Society for Transplantation and Cellular Therapy (ASTCT), formerly American Society for Bone Marrow Transplantation (ASBMT)	Levofloxacin prophylaxis should be considered for adults during neutropenia after HCT to lower risk of Enterobacterales bacteremia Oral penicillin recommended for pneumococcal prophylaxis in patients with chronic graft-versus-host disease (GVHD)

- Levofloxacin has the most supporting evidence in neutropenic patients and provides gram positive coverage
 - Ciprofloxacin may also be used as an alternative

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Freifeld AG et al. Clin Infect Dis. 2011; 52:e56-93.
Tomblin M et al. Biol Blood Marrow Transplant. 2009; 15:1143-1238.
Satlin MJ et al. Transplant Cell Ther. 2021; 27:108-14.

Initial Inpatient Management of Fever in Neutropenic Cancer Patients

- Monotherapy with anti-*Pseudomonas* β -lactam
 - Cefepime
 - Piperacillin-tazobactam
 - Meropenem or imipenem-cilastatin
 - Ceftazidime (not frequently used – no gram-positive activity)
- Considerations when choosing therapy
 - Known colonization with resistant organisms
 - Prior antimicrobial exposure
 - Allergies
 - Presumed site of infection

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Indications for Addition of Expanded Gram-Positive Coverage in Neutropenic Cancer Patients with Fever

- Some gram-positive organisms (e.g., coagulase-negative *Staphylococci*) are intrinsically less virulent than gram negatives and may not need to be treated immediately
- Specific scenarios to add an expanded gram-positive agent (e.g., vancomycin, linezolid)
 - Hemodynamic instability / sepsis
 - Pneumonia
 - Blood culture positive for gram-positive bacteria
 - Clinically suspected CVC infection
 - Skin / soft-tissue infection
 - Colonization with MRSA
 - Severe mucositis only if ceftazidime used AND the patient was on FQ prophylaxis
- Stop the gram positive agent in 2 – 3 days if it is started and no need identified

Freifeld AG et al. *Clin Infect Dis.* 2011; 52:e56-93.

Question 2: Which of the following is the most appropriate antifungal prophylaxis for NV in the immediate post-transplant period?

- A. Fluconazole
- B. Voriconazole
- C. Posaconazole
- D. Isavuconazonium sulfate

Comparison of Azole Antifungals

Antifungal	Half-life (hours)	Bioavailability	Spectrum of Activity		
			Candida	Aspergillus	Mucorales
Fluconazole	31	Excellent	✓ (+/-)	-	-
Voriconazole ^a	6	Variable	✓	✓	-
Posaconazole	25	Poor (suspension) Excellent (tablet)	✓	✓	✓
Isavuconazonium sulfate	130	Excellent	✓	✓	✓

^aVoriconazole half-life and bioavailability are extremely variable

Dodds Ashley ES et al. *Clin Infect Dis* 2006; 43 (suppl 1):S28-39.

Drug Interactions With Azole Antifungals

	Fluconazole	Voriconazole	Posaconazole	Isavuconazonium Sulfate
INHIBITOR				
CYP 3A4	++	++	+++	++
CYP 2C19	+	+++	--	--
CYP 2C9	++	++	--	+++
P-gp	--	--	+	+
SUBSTRATE				
CYP 3A4	+	+	--	+++
CYP 2C19	--	+++	--	--
CYP 2C9	--	+	--	--
P-gp	--	--	+	--

Brüggemann RJ et al. *Clin Infect Dis.* 2009; 48:1441-58.

NCCN Guidelines® for Antifungal Prophylaxis

Risk Group	Predominant Fungal Infections	Recommended Prophylaxis
Low-risk neutropenia (e.g., solid tumors, autologous HSCT without mucositis)	None	None
Autologous HSCT with mucositis	<i>Candida</i> species	1 st line: Fluconazole, micafungin
Allogeneic HSCT (early post HSCT)	<i>Candida</i> species Less commonly mold	1 st line: Fluconazole, micafungin 2 nd line: Voriconazole, posaconazole, amphotericin B formulations
Allogeneic HSCT with significant GVHD	Mold (e.g., <i>Aspergillus</i>) Less commonly <i>Candida</i> species	1 st line: Posaconazole 2 nd line: Voriconazole, echinocandin, amphotericin products
Acute myeloid leukemia / myelodysplastic syndrome on chemotherapy	Mold (e.g., <i>Aspergillus</i>) <i>Candida</i> species	1 st line: Posaconazole 2 nd line: Voriconazole, fluconazole, micafungin, amphotericin B products

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Other Guidelines for Antifungal Prophylaxis in Cancer Patients

- IDSA Guidelines for Antimicrobial Agents in Neutropenic Cancer Patients
 - Prophylaxis against *Candida* is recommended in patients at substantial risk (e.g., allogeneic HSCT recipients, patients receiving intensive induction chemotherapy for acute leukemia)
 - Prophylaxis against *Aspergillus* is recommended in selected patients receiving intensive chemotherapy for acute leukemia
 - Antifungal prophylaxis is not recommended for low risk patients
- ASTCT Guidelines for Preventing Infectious Complications in HCT Recipients
 - Fluconazole and micafungin are preferred for autologous and low-risk allogeneic HCT
 - Voriconazole and posaconazole are preferred for patients with high-risk allogeneic HCT
 - Posaconazole preferred for patients with graft-versus-host disease (GVHD)

Tomblyn M et al. *Biol Blood Marrow Transplant*. 2009; 15:1143-1238.

Freifeld AG et al. *Clin Infect Dis*. 2011; 52:e56-93.

Dadwal SS et al. *Transplant Cell Ther* 2021; 27:201-11

Prophylaxis for *Pneumocystis jirovecii* in Cancer Patients

- Trimethoprim-sulfamethoxazole preferred
- Atovaquone, dapsone, pentamidine (aerosolized / IV) as alternatives if intolerant to trimethoprim-sulfamethoxazole

Risk Group	Disease State	Time Period
High	Allogeneic HSCT	≥ 6 months and while on immunosuppression
	Acute lymphoblastic leukemia (ALL)	Duration of chemotherapy
	Alemtuzumab	≥ 2 months and CD4 > 200 cells/mm ³
	PI3K inhibitors with or without rituximab High dose corticosteroids Temozolomide and radiation	Duration of therapy
Moderate (consider prophylaxis)	Purine analogue therapy or T-cell depletion	Until CD4 > 200 cells/mm ³
	Autologous HSCT	3 – 6 months

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Prophylaxis in recipients of Chimeric Antigen Receptor T-cell (CAR-T) Therapy

- Generally receive lymphodepleting preparative regimens containing fludarabine
- T-cell depletion and steroid use for complications post CAR-T likely increases risk for unusual opportunistic infections, including viral and fungal infections
- No specific guidelines for prophylaxis exist
 - Practice generally mirrors treatment / prophylaxis recommendations in autologous stem cell transplant recipients with T-cell deficiencies
 - Mold-active prophylaxis may be appropriate in patients with complications of CAR-T therapy

Hill JA, Seo SK. *Blood*. 2020; 136:925-35.



Opportunistic Infections in Immunocompromised Patients: Antiviral Prophylaxis and Treatment

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Question 3: Which of the following is the most appropriate choice for antiviral prophylaxis for NV post-transplant?

- A. Valacyclovir and letermovir
- B. Valganciclovir
- C. Foscarnet
- D. Letermovir

Antiviral Prophylaxis in Cancer Patients

Viral Infection	Recommended Antiviral Agents	Prophylaxis Recommendations
Herpes simplex virus (HSV)	Acyclovir Famciclovir Valacyclovir	<ul style="list-style-type: none"> HSV-seropositive patients receiving chemotherapy for acute leukemia Allogeneic and autologous HSCT recipients during neutropenia or GVHD
Varicella zoster virus (VZV)	Acyclovir Famciclovir Valacyclovir	<ul style="list-style-type: none"> Allogeneic HSCT recipients for ≥ 1 year (longer if GVHD present) Patients receiving proteasome inhibitors or alemtuzumab Consider in autologous HSCT recipients for 6-12 months
Cytomegalovirus (CMV)	None (preemptive therapy preferred) Consider letermovir (HSCT only)	<ul style="list-style-type: none"> CMV-seropositive allogeneic HSCT recipients Patients receiving alemtuzumab

- Consider prophylaxis for HSV and VZV in other intermediate-risk groups (e.g., lymphoma, autologous HSCT, multiple myeloma, chronic lymphocytic leukemia, purine analogue therapy)

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Tomblin M et al. *Biol Blood Marrow Transplant*. 2009; 15:1143-1238.
Hakki M et al. *Transplant Cell Ther* 2021;27:707-19.

CMV Prevention in HSCT Recipients

- ASTCT: All CMV seropositive (i.e., donor and/or recipient with evidence of past CMV infection) allogeneic HCT recipients should receive letermovir prophylaxis through day 100 (ASTCT)
- NCCN: Consider letermovir through day 100 in CMV-seropositive HCT recipients, otherwise perform weekly screening / pre-emptive therapy
- Patients with evidence of asymptomatic viral reactivation require treatment (more on this later)
 - End-organ disease is now rare with routine monitoring and treatment

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Tomblyn M et al. *Biol Blood Marrow Transplant*. 2009; 15:1143-1238.

Letermovir as Antiviral Prophylaxis in CMV-Seropositive Allogeneic HSCT Recipients

- Letermovir is a novel CMV antiviral agent that was approved by the FDA in 2017 and is available in IV and oral formulations
 - Mechanism: inhibits CMV terminase complex, preventing successful viral replication
- Active only against CMV
 - Key point: other antiviral prophylaxis remains required in patients receiving letermovir
- Phase III clinical trial demonstrated lower risk of clinically significant CMV infections in CMV-seropositive allogeneic HSCT recipients through week 24 relative to placebo (60.6% vs. 37.5%, $p < 0.001$)

Marty FM et al. *N Engl J Med.* 2017; 377:2433-2444.

Antiviral Prophylaxis in Solid Organ Transplant Recipients

Viral Infection	Recommended Antiviral Agents	Prophylaxis Recommendations
Herpes simplex virus (HSV)	Acyclovir OR Famciclovir OR Valacyclovir OR CMV Prophylaxis (if indicated)	<ul style="list-style-type: none"> Administer at least 1 month post transplant Administer at least 1 month during treatment of rejection
Varicella zoster virus (VZV)	Acyclovir Valacyclovir	<ul style="list-style-type: none"> Consider if not receiving HSV or CMV prophylaxis, but not well-studied
Cytomegalovirus (CMV)	Valganciclovir OR Ganciclovir intravenous OR Serial monitoring with preemptive therapy	<ul style="list-style-type: none"> Low-risk (donor - / recipient -): no specific prophylaxis Intermediate risk (D-/R+): Prophylaxis versus pre-emptive therapy High risk (D+/R-): Prophylaxis for 3 – 6 months (some cases more)

Wilck MB et al. *Am J Transplant.* 2013; 13:121-7.
Pergam SA et al. *Am J Transplant.* 2013; 13:138-46.
Kotton CN et al. *Transplantation.* 2018; 102:900-931.

Key Points in Antimicrobial Prophylaxis

- Prophylaxis must be tailored to individual patient risks and depth / duration of immunosuppression
 - e.g., allogeneic HCT with significant GVHD warrants anti-mold prophylaxis
- Choice and duration of therapy is center and patient-risk specific
 - e.g., pre-emptive therapy and universal prophylaxis are both viable CMV prevention strategies in cardiac transplant
- Therapy is frequently modified due to drug-drug interactions, adverse effects, and cost considerations
 - e.g., voriconazole and posaconazole have differing drug interaction profiles
- Guidelines frequently serve as a starting point for discussion for individual programs

Case Continues

- NV is now 4 months (130 days) post transplantation and remains in remission
- She has developed Grade III of IV acute GVHD of the colon, managed with prednisone 40 mg orally daily and tacrolimus 3 mg orally every 12 hours
- She presents to the emergency department with severe non-bloody diarrhea and abdominal cramping
- A serum CMV PCR performed at the time of admission revealed a viral load of 18,786 international units/mL

Case Continues

- Current medications:
 - Levofloxacin 500 mg orally twice daily
 - Posaconazole 300 mg orally daily (changed from fluconazole)
 - Valacyclovir 500 mg orally daily
 - Trimethoprim/sulfamethoxazole 1 DS tab orally MWF
 - Tacrolimus 3 mg orally every 12 hr
 - Prednisone 40 mg orally daily
 - Loperamide 2 mg orally as needed for diarrhea
 - Ondansetron 4 mg orally as needed for nausea/vomiting
 - Pantoprazole 40 mg orally daily
 - Acetaminophen 325 mg orally every 4 hr as needed for pain

Case Continues

- BP: 112/78 mmHg HR: 124 beats/min T: 39.4°C
RR: 24 breaths/min O₂ Sat: 97% RA
Wt: 53.8 kg
- Imaging: notable only for pericolic stranding
- Gen: Awake, significantly distressed, complaining of constant pain
- Physical: Notable for significant abdominal pain and tenderness, bowel sounds hyperactive throughout
- Pertinent labs:
 - WBC: 4.1×10^3 cells/mm³ (83% neutrophils, 6% lymphocytes)
 - SCr: 2.9 mg/dL (was 0.8 mg/dL last week), K 3.1mg/dL, ionized Ca: 0.5 mg/dL

Question 4: Which of the following is the best antiviral choice for initial treatment of CMV in NV?

- A. Acyclovir
- B. Foscarnet
- C. Ganciclovir
- D. Letermovir

Foscarnet Versus Ganciclovir for CMV Reactivation in HSCT Recipients

- One multicenter, international randomized trial compared preemptive therapy for allogeneic HSCT recipients with CMV reactivation within 100 days post-transplant
 - 218 patients randomly assigned to open-label foscarnet or ganciclovir
 - Evidence of CMV reactivation by PCR or *pp65* antigenemia without evidence of CMV end-organ disease
- Full-dose treatment continued for 2 weeks followed by 2 weeks of reduced-dose maintenance therapy

Reusser P et al. *Blood*. 2002; 99:1159-64.

Results

Outcome (%)	Foscarnet (n = 110)	Ganciclovir (n = 103)
Event-free survival	66	73
Overall mortality	26	22
Development of CMV disease	5	5
<i>Pneumonia</i>	3	2
<i>Gastrointestinal</i>	2	2
<i>Retinitis</i>	0	1
Premature discontinuation due to adverse event during induction	2	5
Premature discontinuation due to adverse event during maintenance	0	3
Retreatment required	43	28
Severe neutropenia	4	11
Acute kidney injury	5	2

- Electrolyte abnormalities significantly more common in foscarnet-treated patients

Reusser P et al. *Blood*. 2002; 99:1159-64.

Conclusions

- Foscarnet and ganciclovir are similarly effective in the treatment of early CMV reactivation in HSCT recipients
- Ganciclovir associated with more frequent myelosuppression than foscarnet
- Foscarnet associated with more frequent renal toxicity and electrolyte abnormalities than ganciclovir
- Choice of therapy depends on patient risk factors and tolerance for disparate toxicities
 - Foscarnet may be preferred if patient has myelosuppression or at high risk for myelosuppressive adverse events
 - Ganciclovir may be preferred if patients has renal / electrolyte abnormalities

Reusser P et al. *Blood*. 2002; 99:1159-64.

CMV Treatment in Allogeneic HCT Recipients

- NCCN Guidelines® and ASTCT Guidelines
 - Ganciclovir or valganciclovir are both acceptable first-line options for pre-emptive therapy in HSCT recipients and preferred in most situations
 - Valganciclovir should not be used in patients with significant (Grade III / IV) gastrointestinal GVHD
 - Foscarnet may be used as an alternative to ganciclovir or valganciclovir in situations where (val)ganciclovir cannot be used
- Treatment should generally continue for a minimum of 2 weeks until DNAemia clearance, followed by secondary prophylaxis with valganciclovir or letermovir
- Screening should continue until at least D +180 in patients who receive letermovir primary prophylaxis

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Treatment of CMV in Solid Organ Transplant Recipients

- Non-severe disease
 - Valganciclovir is preferred unless concern for poor absorption of oral medications or low adherence
 - Ganciclovir is alternative
- Severe disease
 - Intravenous ganciclovir is preferred
- Dose reduction due to adverse events (e.g., myelosuppression) is not recommended to avoid development of resistance
 - Change in therapy is preferred
- Therapy should be continued for ≥ 2 weeks and until screening assays are negative

Kotton CN et al. *Transplantation*. 2018; 102:900-931.

Case Continues

- Three days after initiating ganciclovir, NV's diarrhea improved significantly with resolution of abdominal pain and acute kidney injury
- A CMV viral load sent on day 9 after presentation is negative, and she is sent home with a prescription for valganciclovir 900 mg PO BID for 6 more days to be followed by 900 mg PO daily as secondary prophylaxis
- Two weeks into secondary prophylaxis, diarrhea recurs and a CMV serum viral load is positive at 4,654 international units/mL
- A CMV genotype reveals a mutation in the *UL97* gene with no mutations present in *UL54*

Question 5: Which of the following is the most appropriate antiviral treatment for this resistant CMV in NV?

- A. Foscarnet
- B. High-dose ganciclovir
- C. Letermovir
- D. Cidofovir

Treatment of Antiviral Resistant CMV

- *UL97* mutations generally confer resistance to ganciclovir and valganciclovir
 - *UL97* encodes viral kinase that phosphorylates ganciclovir
 - Cidofovir and foscarnet do not rely on *UL97* kinase for activity
 - First line: foscarnet, second line: cidofovir
 - Consider investigational agents such as maribavir or CMV-specific cytotoxic T-cell infusion) recommended
- *UL54* mutations may confer resistance to any or all of foscarnet, ganciclovir, valganciclovir, and cidofovir
 - Treatment of choice highly dependent on specific mutation present

El Chaer F et al. *Blood*. 2016; 128:2624-36.
Yong MK et al. *Transplant Cell Ther* 2021; ePub ahead of print.

Case Continues

- NV is successfully treated for CMV colitis with foscarnet and returns home on daily maintenance foscarnet
- Due to a change in insurance, her posaconazole copayment increases to \$300 / month and she does not pick up his prescription
- Three weeks after discharge, she develops shortness of breath and severe pleuritic chest pain
- A chest x-ray performed in clinic reveals a right upper lobe opacity and he is placed on meropenem and vancomycin with a presumptive diagnosis of pneumonia
- Two days later, a serum galactomannan obtained in clinic returns with a value of 2.4 GMI



Opportunistic Infections in Immunocompromised Patients: Invasive Fungal Infections

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Question 6: Which of the following best supports the diagnosis of invasive aspergillosis in NV?

- A. Positive serum galactomannan
- B. Yeast in sputum culture
- C. Opacity on chest x-ray
- D. Pleuritic chest pain

Diagnostic Criteria for Invasive Fungal Infections (IFI)

Category	Criteria
Proven	Direct pathologic evidence or culture from sterile site
Probable	Compatible host AND Clinical and/or radiologic findings AND Culture from non-sterile site OR Indirect serologic evidence
Possible	Compatible host AND Clinical and/or radiologic findings WITHOUT Mycologic evidence

- Standard diagnostic criteria from the European Organisation for Research and Treatment of Cancer / Mycoses Study Group (EORTC / MSG)
- Criteria are not specific to any one fungus

Donnelly JP et al. *Clin Infect Dis.* 2019; 71:1367-76.

Host Criteria for IFI

- EORTC / MSG definitions
 - Recent history of prolonged neutropenia (<500 cells/mm³) or hematologic malignancy
 - Receipt of an allogeneic HSCT or solid organ transplant
 - Prolonged use of corticosteroids at a minimum dose of 0.3 mg/kg/day prednisone equivalent for >3 weeks
 - Treatment with T-cell or B-cell immunosuppressants within the last 90 days
 - Inherited severe immunodeficiency
 - CD4 lymphopenia (cryptococcosis, pneumocystis only)
- IFI can occur in the absence of these risk factors
- Individual patient risks and cumulative immunosuppression should be considered

Donnelly JP et al. *Clin Infect Dis*. 2019; 71:1367-76.

Clinical Criteria for IFI

Category	Criteria
Lower respiratory tract	Dense, well circumscribed lesions OR Air-crescent sign OR Cavity OR Wedge-shaped, segmental/lobar consolidation OR Reverse halo sign
Sinonasal infection	Sinusitis on imaging AND acute localized pain OR Nasal ulcer with black eschar OR Extension from sinus across bone
Central nervous system	Focal lesions on imaging Meningeal enhancement on imaging

- High-resolution preferred modalities to identify IFI

Donnelly JP et al. *Clin Infect Dis.* 2019; 71:1367-76.

Diagnosis of Invasive Aspergillosis (IA)

- *Aspergillus* is a ubiquitous mold found in the environment
- The most common invasive mold infection in immunocompromised patients
- Indirect serum tests for invasive aspergillosis
 - Galactomannan – component of *Aspergillus* cell wall released into systemic circulation in angioinvasive disease
 - Serum and/or bronchoalveolar lavage galactomannan recommended as diagnostic marker for IA in patients with hematologic malignancy
 - Not recommended for screening in non-neutropenic patients or patients receiving mold-active prophylaxis
 - Cross-reactivity possible with *Fusarium*, *Scedosporium*, other less common molds
 - (1 → 3)- β -D-glucan – component of cell wall in many fungi
 - Recommended for patients at high risk for IA
 - Not specific for *Aspergillus*
 - High rate of false positivity due to cross-reactivity with yeast (including *Candida*), numerous medications, and laboratory error

Patterson TF et al. *Clin Infect Dis*. 2016; 63:e1-60.

Question 7: Which of the following is the best antifungal treatment for invasive aspergillosis in NV?

- A. Voriconazole
- B. Anidulafungin
- C. Liposomal amphotericin B
- D. Posaconazole

Voriconazole Versus Amphotericin B Deoxycholate for Invasive Aspergillosis

- International, multicenter, randomized, Phase III non-inferiority trial of patients with definite or probable invasive aspergillosis
 - Not limited to patients with hematologic malignancy
 - Both pulmonary and non-pulmonary invasive aspergillosis included
- Patients randomized to:
 - Voriconazole IV for at least 7 days followed by oral voriconazole or amphotericin B deoxycholate
 - Change to other licensed antifungal treatment allowed in cases of intolerance to study drug
- Primary end-point:
 - Overall successful outcome at week 12 in patients
 - Assessed in patients with definite / probable IA and received one dose of study drug

Herbrecht R et al. *N Engl J Med*. 2002; 347:408-15.

Efficacy Results

Outcome (%)	Voriconazole (n = 144)	Amphotericin B deoxycholate (n = 133)
Successful outcome	52.8	31.6
<i>Complete response</i>	20.8	16.5
<i>Partial response</i>	31.9	15.0
Unsuccessful outcome	47.2	68.4
<i>Stable disease</i>	5.6	6.0
<i>Failure of therapy</i>	38.2	58.6
<i>Indeterminate</i>	3.5	3.8
Survival	70.8	57.9

- Absolute difference in success 21.2% (95% CI 10.4 to 32.9%), indicating statistical superiority of voriconazole
- Hazard ratio for overall survival: 0.59 (95% CI 0.40 to 0.88) favoring voriconazole

Herbrecht R et al. *N Engl J Med*. 2002; 347:408-15.

Safety Results

Outcome (n, %)	Voriconazole (n = 194)	Amphotericin B deoxycholate (n = 185)	P-value
Visual disturbances	87 (44.8)	8 (4.3)	<0.001
Hallucinations / confusion	13 (6.7)	5 (2.7)	0.09
Skin reactions	16 (8.2)	6 (3.2)	0.05
Chills / fever	6 (3.1)	46 (24.9)	<0.001
Renal impairment	2 (1.0)	19 (10.3)	<0.001
Hypokalemia	0	6 (3.2)	0.01

- Number of adverse events related to study drug significantly less common in voriconazole group despite longer median duration of treatment with voriconazole

Herbrecht R et al. *N Engl J Med.* 2002; 347:408-15.

Conclusions and Implications

- Voriconazole is superior to amphotericin B deoxycholate for treatment of invasive aspergillosis
- Median duration of treatment with voriconazole (77 days) longer than amphotericin B deoxycholate (10 days) due primarily to differences in tolerability
- Results are generally considered to be applicable to other amphotericin formulations (e.g., liposomal amphotericin B, amphotericin B lipid complex)

Herbrecht R et al. *N Engl J Med.* 2002; 347:408-15.

Guidelines for Treatment of Invasive Aspergillosis

	IDSA	ASTCT
First line	Voriconazole	Voriconazole
Second-line	Isavuconazonium sulfate, liposomal amphotericin B	Isavuconazonium sulfate, posaconazole, liposomal amphotericin B
Salvage	Amphotericin B lipid complex, echinocandin, posaconazole	N/A

- Major difference is placement of posaconazole
 - Related to timing of release of guidelines and publication of posaconazole Phase III trial for invasive aspergillosis

Patterson TF et al. *Clin Infect Dis*. 2016; 63:e1-60.
Dadwal SS et al. *Transplant Cell Ther* 2021; 27:201-11.

Is there a role for front-line combination therapy for invasive pulmonary aspergillosis?

- One prospective, randomized trial compared voriconazole with anidulafungin versus voriconazole alone
 - Overall mortality at 6 weeks was 19.3% in combination arm versus 27.5% in monotherapy arm ($p = 0.087$)
 - Post-hoc analysis suggested statistical benefit in subgroup diagnosed by galactomannan positivity
- IDSA guidelines: “suggest consideration for an echinocandin with voriconazole for primary therapy in the setting of severe disease, especially in patients with hematologic malignancy and those with profound and persistent neutropenia”

Patterson TF et al. *Clin Infect Dis*. 2016; 63:e1-60.
Marr KA et al. *Ann Intern Med*. 2015; 162:81-9.

Case Continues

- Four days after starting voriconazole, NV begins to experience visual hallucinations and claims to see Bob Ross having a conversation with Mr. Rogers in her room. She also complains of floaters and bright light flashes. She realizes all of these are hallucinations and has no alterations in mental status.
- A trough concentration of voriconazole obtained immediately prior to his last dose returns 4 days later with a value of 6.5 mg/dL

Question 8: Which of the following is the generally recommended trough serum concentration for voriconazole?

- A. < 1 mcg/mL
- B. > 5.5 mcg/mL
- C. > 3 mcg/mL
- D. > 1 mcg/mL

Therapeutic Drug Monitoring (TDM) of Azole Antifungals – British Society of Mycology Guidelines

Drug	Minimum Trough	Maximum Trough	Timing Relative to Initiation of Therapy or Dose Modification
Voriconazole	Prophylaxis: undefined Therapeutic: >1 mcg/mL	All indications: <4 to 6 mcg/mL	2 to 5 days
Posaconazole	Prophylaxis: >700 ng/mL Therapeutic: > 1,000 ng/mL	All indications: undefined	> 7 days

- Quality of evidence supporting TDM ranges is low
- Unclear whether therapeutic ranges are applicable to tablet and intravenous formulations of posaconazole with improved bioavailability
- No data supporting utility of TDM for isavuconazonium sulfate

Ashbee R et al. *J Antimicrob Chemother.* 2014; 69:1162-76.

Question 9: Which is the best alternative treatment strategy for NV at this time?

- A. Fluconazole
- B. Isavuconazonium sulfate
- C. Caspofungin
- D. Amphotericin B Lipid Complex

New Kids On the Block: Isavuconazole and Posaconazole

- Voriconazole has now been compared to posaconazole and isavuconazonium sulfate in two Phase III, international, double-blind, non-inferiority studies for the treatment of invasive *Aspergillus*
- Primary end-point in both studies:
 - All-cause mortality 42 days
- Neither study allowed therapeutic drug monitoring

Maertens JA et al. *Lancet*. 2016; 387:760-769.
Maertens JA et al. *Lancet* 2021; 397: 499-509.

Key Phase III Trial Results

Outcome (n, %)	Isavuconazonium sulfate vs Voriconazole		Posaconazole vs Voriconazole	
	Isavuconazonium sulfate	Voriconazole	Posaconazole	Voriconazole
	n = 258	n = 258	n = 288	n = 287
Day 42 all-cause mortality	48 (19)	52 (20)	44 (15)	59 (21)
Toxicity				
Skin / subcutaneous tissue disorders	86 (33)	110 (42)	5 (2)	12 (4)
Eye disorders	39 (15)	69 (27)	5 (2)	28 (10)
Hepatobiliary disorders	23 (9)	42 (16)	9 (3)	10 (3)
Skin / subcutaneous tissue disorders	86 (33)	110 (42)	5 (2)	12 (4)

- Both posaconazole and isavuconazole deemed non-inferior to voriconazole
- Both with favorable adverse-event profiles relative to voriconazole

Maertens JA et al. *Lancet*. 2016; 387:760-769.
Maertens JA et al. *Lancet* 2021; 397: 499-509.

Conclusions and Implications

- Posaconazole and isavuconazonium sulfate non-inferior to voriconazole for treatment of invasive pulmonary aspergillosis
- Both posaconazole and isavuconazonium sulfate appear to be better-tolerated than voriconazole
- Unclear whether voriconazole TDM would have influenced these results
- Voriconazole remains drug of choice per guidelines, suspect this will not remain the case

Maertens JA et al. *Lancet*. 2016; 387:760-769.
Maertens JA et al. *Lancet* 2021; 397: 499-509.

Invasive Mucormycosis

- Mucormycosis refers to a group of ubiquitous environmental molds (e.g., *Rhizopus*, *Mucor*, *Rhizomucor*)
- Relatively uncommon compared with *Aspergillus*, but increasing worldwide
 - Possibly due to widespread use of anti-mold prophylaxis in high risk patients
- Causes rapid, destructive disease in compatible hosts, but rarely affects patients without significant immunocompromise
 - Relapsed leukemia, high-risk allogeneic HSCT, severe GVHD, and others
- Intrinsically less susceptible to antifungal agents than other invasive molds

Kontoyiannis DP, Lewis RE. *Blood*. 2011; 118:1216-24.

Differentiation of Invasive Mucormycosis From Invasive Aspergillosis

- Epidemiologic / host factors
 - Institution / geographic location with high rate of mucormycosis
 - Iron overload
 - Prior treatment with voriconazole or echinocandins
- Clinical / radiologic / laboratory factors
 - Community-onset sinusitis
 - Necrotic lesions in hard palate or nasal turbinates
 - Chest wall cellulitis next to lung infarct
 - >10 nodules on chest CT scan
 - Reverse halo sign on chest imaging
 - Presumptive diagnosis of IFI with therapeutic voriconazole levels
 - Presumptive diagnosis of IFI with negative serum biomarkers

Kontoyiannis DP, Lewis RE. *Blood*. 2011; 118:1216-24.

Treatment of Invasive Mucormycosis

- Liposomal amphotericin B is cornerstone of treatment
 - 5 – 10mg/kg i.v. daily; utility of doses >5mg/kg remains controversial
- Posaconazole and isavuconazonium sulfate alternatives for patients with pre-existing renal insufficiency
 - Limited data supporting their primary use
- Combination therapy with liposomal amphotericin B + azole +/- echinocandin often used clinically with minimal supporting data
- Surgical débridement recommended in addition to antifungal therapy whenever feasible
- Treatment duration dependent on resolution of host immune factors

Cornely OA et al. *Lancet Infect Dis.* 2019; ePub ahead of print.

Considerations in Treatment of IFI

- All randomized controlled trials exclude patients receiving mold-active prophylaxis
 - Limits applicability in most patients receiving guideline-recommended prophylactic agents
- Extremely limited data to guide treatment of breakthrough IFI in patients receiving mold-active prophylaxis
- An individualized approach based on patient risks and presumptive diagnosis is warranted

Conclusions

- Prophylactic, preemptive, and treatment strategies for opportunistic infections in immunocompromised patients should be tailored to meet individual needs
- Infectious diseases pharmacists play an important role in recommending antibacterial, antifungal, and antiviral therapies in these patients

Opportunistic Infections in Immunocompromised Patients

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