Invasive fungal infections: What to do if there's a fungus among us

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This speaker has no conflicts to disclose

Objectives (Pharmacists)

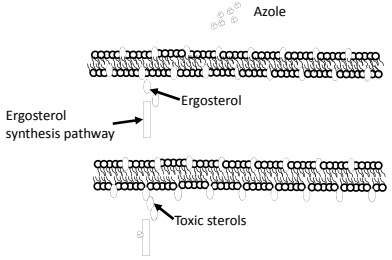
- List three important interactions and monitoring parameters for a given antifungal agent
- Identify two scenarios where empiric antifungal therapy is warranted
- Identify drug(s) of choice for at least one invasive fungal infection

Objectives (Technicians)

- Describe the importance of utilizing an antifungal stewardship program
- State the most commonly used antifungal agents in the hospital setting
- When given a specific pathogen, list the most common antifungal agent(s) used to treat the infection.

Azoles: Mechanism of action

- Inhibit the synthesis of ergosterol, a vital component of the fungal cell membrane



Commercially Available Azoles

- Fluconazole
- Voriconazole
- Itraconazole
- Posaconazole
- Isavuconazole

Fluconazole: Dosing and Administration

- Available as IV or PO tablets
- Dosing ranges from 400-800mg (or 6-12mg/kg) once daily depending on indication and immune status
  - Lower doses are used for candiduria or esophageal candidiasis
- Doses should be reduced by 50% in patients on hemodialysis, CRRT, or with CrCl $\leq$50

Fluconazole package insert. Pfizer; 2014.

Fluconazole: Spectrum

- Fluconazole has reliable activity against most types of *Candida* spp.
  - *C. glabrata* has variable resistance to all azoles, may require aggressive dosing
  - *C. krusei* is intrinsically resistant to fluconazole
- Also has activity against *Cryptococcus* spp.

Clin Infect Dis 2006;43:S28-39.

Fluconazole: Susceptible-Dose Dependent

- *Candida* spp. Isolates with MICs of 16 or 32 are considered susceptible dose-dependent
  - Fluconazole doses of 400-800 mg/day should be used for these isolates
- Fluconazole AUC/MIC ratios of 25 mg·hr/L have been associated with efficacy
- In healthy 70 kg patients doses of 400 mg correlate with an AUC of ~400 mg·hr/L

Clin Microbiol Rev 2006; 19: 435-447

Fluconazole: Interactions and ADEs

Inhibits	CYP 2C9 (strong), 2C19 (strong), 3A4 (moderate)
	• Phenytoin • Warfarin • Dofetilide • Sirolimus • Citalopram
Substrate	N/A Rifampin may decrease serum concentrations
ADEs	• Headache • N/V/D • LFT abnormalities • Additive QTc prolongation (especially in patients receiving ≥400mg/day)

Fluconazole package insert. Pfizer; 2014.

Voriconazole: Spectrum of Activity

- Voriconazole has reliable activity against *Aspergillus* spp., *Candida* spp., as well as *Fusarium* spp.
  - Some studies report variable in vitro susceptibility of *C. glabrata*

Antimicrob Agents Chemother. 1998;42:161-3.
J Antimicrob Chemother. 1999;44:697-700.
J Antimicrob Chemother. 1998;42:253-6
Clin Infect Dis 2006;43:S28-39.

Voriconazole: Dosing and Administration

- Available as IV and PO tablets
- IV dosing is weight based
  - 6mg/kg q12h for 2 doses, then 4mg/kg q12h
- PO dosing is standardized
  - 100mg q12h for patients <40 kg
  - 200mg q12h for patients ≥40 kg
- Dosing should be reduced by 50% in patients with mild to moderate liver dysfunction (Childs-Pugh class A or B)
  - In severe liver dysfunction this should only be used if the benefits outweigh the risk

Voriconazole package insert. Pfizer; 2014.

Voriconazole and Renal Dysfunction

- Voriconazole is not renally cleared
  - No dosage adjustment for renal dysfunction
- Per package insert:
  - Avoid IV administration in patients with a creatinine clearance < 50 mL/min
- Why is this?

Voriconazole package insert. Pfizer; 2014.

Cyclodextrin toxicity

- Cyclodextrin is a solvent agent used in the formulation of IV voriconazole
- Pharmacokinetic data have shown that its clearance is directly correlated with renal function
  - Accumulates even in patients on HD, CRRT and PD
- Data from animal studies suggest accumulation of cyclodextrin can lead to renal and hepatic dysfunction

IV Voriconazole in Renal Impairment

Population (n=128)	Retrospective review of patients receiving fluconazole (n=54), caspofungin (n=55) or voriconazole (n=19) who had CrCl <50 at the time of administration.
Rate of AKI	Rates of AKI were higher in the fluconazole group than for the caspofungin group (p=0.01) however rates of AKI in the voriconazole group was not significantly different
Logistic Regression analysis of causes related to AKI	In a multivariate logistic regression identified only infecting organism as associated with development of AKI
Conclusions	In multivariate analysis of patients with invasive fungal infections and renal dysfunction at baseline, IV voriconazole was not associated with increased risk of AKI

BMC Infect Dis 2013; 13: 14.

Voriconazole: Interactions and ADEs

Inhibits	CYP 3A4 (strong), 2C9 (strong), 2C19 (strong)
	• Cyclosporine (Reduce dose by 50%) • Statins (switch to non-CYP metabolized) • Sirolimus (Reduce dose by 90%) • Phenytoin (Reduce dose by 50%, increase voriconazole dose to 400mg PO or 5mg/kg IV) • Tacrolimus (Reduce dose by 66%) • Warfarin (monitor, may require decrease in dose)
Substrate	CYP 3A4, 2C9, 2C19
ADEs	• Visual disturbances • Increased LFTs • Increased SCr • QTc prolongation

Voriconazole package insert. Pfizer; 2014.

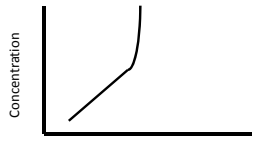
Voriconazole Therapeutic Drug Monitoring

- Voriconazole therapeutic drug monitoring has been associated with improved outcomes and decreased adverse events
- Target troughs: 1-5.5 mg/L
  - Troughs <1 mg/L associated with lack of response in Aspergillosis
  - Troughs > 5.5 mg/L associated with toxicity

Clin Infect Dis 2008; 46: 201-211.
Clin Infect Dis 2012; 55: 1080-1087

Voriconazole Dosing

CAUTION



Non-Linear Pharmacokinetics

Posaconazole: Dosing and Administration

- Now available as oral solution, tablet and IV formulation
- Dosing differs based on indication and formulation used
- **Delayed release tablets and IV solution are currently only FDA approved for fungal prophylaxis**

Formulation	Loading Dose	Maintenance Dose
Oral: Solution	200 mg QID until disease stabilization	400 mg BID
Oral: Delayed Release Tablets	300 mg BID x2 doses	300 mg daily
Intravenous Solution	300 mg BID x2 doses	300 mg daily

Posaconazole: Oral Solution

- Poor absorption and bioavailability
  - Must administer with high fat meal or low pH drink
  - Avoid with administration of antacids
    - Decreases AUC by 32-39%
  - Saturable absorption
    - Max dose 800 mg/day divided 2-4x
  - Absorption decreased in patients with diarrhea and mucositis

Posaconazole package insert. Pfizer; 2014.
Antimicrob Agents Chemother 2009; 53: 24-34.
Antimicrob Agents Chemother 2009; 53: 24-5224-5229.

Posaconazole: Delayed Release Tablet

- Good absorption independent of administration with food
- Less affected by antacids
- 200 mg dose results in average concentrations of 1300 ng/mL
  - Healthy patients
- Substantial accumulation by day 14
  - AUC increased 3x from day 1 to day 14

Posaconazole package insert. Pfizer; 2014.
J Antimicrob Chemother 2012; 67: 2725-2730.

Posaconazole: IV Formulation

- Increased exposure relative to tablets on day 1
- Cyclodextrin used for solubility
  - Per package insert:
    - Should be avoided in patients with CrCl < 50 ml/min unless the benefit outweighs the risk

Posaconazole package insert. Pfizer; 2014.
Antimicrob Agents Chemother 2014; 59: 1246-1251.

Posaconazole: Spectrum of Activity

- Posaconazole is active against all clinically relevant yeasts and molds
  - *In vitro* studies suggest variable resistance with *C. glabrata*

Clin Infect Dis 2006;43:528-39.

Posaconazole: Interactions and ADEs

Inhibits	CYP 3A4 (strong)
	A number of drugs are contraindicated with posaconazole including: • Simvastatin • Sirolimus • 3A4 substrates that may prolong QTc
Substrate	N/A
ADEs	• N/V/D • Fever • Headache • Hypokalemia • Increased LFTs • QTc prolongation • Thrombophebitis (IV only) • Infusion reactions (IV only)

Posaconazole package insert. Pfizer; 2014.

Posaconazole Therapeutic Drug Monitoring

- Posaconazole shows substantial interpatient variability
- Clinical studies have shown correlation between posaconazole levels and efficacy
  - Currently limited to studies of oral solution
- Goal troughs
  - Prophylaxis: > 700 ng/mL
  - Treatment: > 700 ng/mL, can increase to > 1250 ng/mL based on clinical response

Antimicrob Agents Chemother 2009; 53: 24-34.

The new kid on the block: Isavuconazole

- Isavuconazole is a newly approved azole antifungal with broad activity against fungi and molds
- Administered as the prodrug isavuconazonium sodium
  - Rapidly cleaved to active drug via plasma esterases
- FDA approved for the treatment of Aspergillosis and Mucormycosis

Isavuconazole package insert. Astellas; 2015

Isavuconazole: Dosing and Administration

- Available as IV solution and oral capsules
  - Highly bioavailable
- No dose adjustments for renal dysfunction or Childs-Pugh class A or B liver dysfunction

Indication	Loading Dose	Maintenance Dose
Treatment of Aspergillosis or Mucormycosis	372 mg isavuconium sulfate every 8 hours x 6 doses	372 mg isavuconium sulfate daily (12-24h post maintenance doses)

Isavuconazole package insert. Astellas; 2015

Isavuconazole: Spectrum of Activity

- MIC breakpoints for isavuconazole have not yet been established
- Based on in vitro data, isavuconazole appears to have activity against most clinically relevant yeasts and molds
  - Active against Mucorales, variable based on species
  - Limited activity against *Fusarium spp.*

Isavuconazole package insert. Astellas; 2015.
Clin Infect Dis 2015; Online Access.

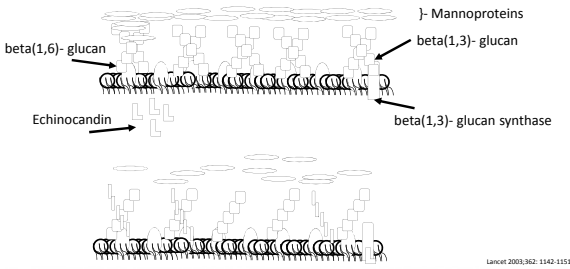
Isavuconazole: Interactions and ADEs

Inhibits	CYP 3A4 (moderate) Induces CYP 2B6
	• Sirolimus • Midazolam • Tacrolimus 2B6 Substrates • Bupropion
Substrate	CYP 3A4 Contraindicated with strong inhibitors or inducers
ADEs	• N/V/D • Headaches • Hypokalemia • Abdominal pain • Increased LFTs

Isavuconazole package insert. Astellas; 2015

Echinocandins: Mechanism of Action

- Inhibit the formation of β-(1,3)-glucan, an important part of the fungal cell wall



Lancet 2003;362: 1142-1151.

Echinocandins: Spectrum of Activity

- All echinocandins have similar spectrums of activity
- Active against *Candida* spp., including *C. glabrata* and *C. krusei*
  - Echinocandins have variable *in vitro* activity against *C. parapsilosis**
- Limited activity against *Aspergillus* spp.
  - Fungistatic
  - May be appropriate in salvage therapy

Lancet 2003;362: 1142-1151.

Echinocandins: Dosing and Administration

- All commercially available echinocandins are IV only

Drug	Loading Dose	Maintenance Dose
Caspofungin	70mg x 1	50mg daily
Micafungin	None	100mg daily
Anidulafungin	200mg x1	100mg daily

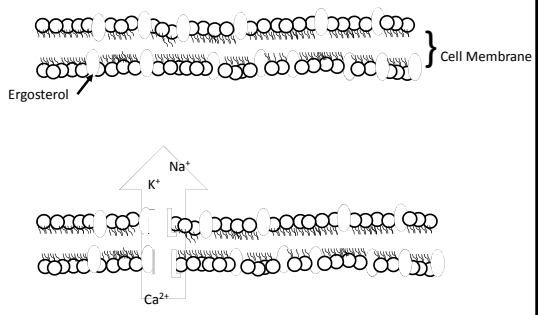
Expert Opin Infect Dis 2003; 12: 1313-1333.

Echinocandins: Interactions and ADEs

Inhibits	Micafungin- CYP 3A4 (minor)
Substrate	Micafungin- CYP 3A4 (minor)
Avoid with concurrent use of	Micafungin may increase levels of sirolimus, usually is not clinically relevant, however monitoring is warranted
ADEs	• LFT elevations • Fever • N/V/D • Hypomagnesemia • Hypokalemia

Lancet 2003;362: 1142-1151.
Expert Opin Infect Dis 2003; 12: 1313-1333.

Amphotericin: Mechanism of Action



Drugs 2009; 69: 361-392.

Amphotericin: Spectrum of Activity

- Amphotericin has activity against most clinically relevant yeasts and molds
  - Variable activity against:
    - *Fusarium* spp.
    - *Zygomycetes*
  - Important gaps in coverage include:
    - *Aspergillus terreus*
    - *Candida lusitaniae*

Clin Infect Dis 2006;43:S28-39.
Drugs 2009; 69: 361-392.

Amphotericin: Dosing and Administration

- Amphotericin B is only commercially available as IV formulation
- Dosing depends on formulations
  - Amphotericin B deoxycholate- 0.6-1.5mg/kg
  - Lipid formulations- generally 3-5 mg/kg
    - Liposomal amphotericin B has been studied in doses up to 12 mg/kg

Drugs 2009; 69: 361-392.
Clin Infect Dis 2007; 44: 1289-1297.

Amphotericin: Interaction and ADEs

Inhibits	N/A
Substrate	N/A
Avoid with concurrent use of	• Other nephrotoxic agents
ADEs	• Renal dysfunction • Infusion reactions • N/V/D • Pulmonary toxicities • Hypokalemia • Hypomagnesemia

- Lipid formulations have been shown to be equally efficacious for most indications
- Lower rates of side effects- especially nephrotoxicity
  - Rates of infusion reactions similar!

Drugs 2009; 69: 361-392.

Antifungal Stewardship

- Unnecessary antifungal therapy can lead to increased costs, ADEs and increased resistance
- Antifungal stewardship has been shown to decrease the number of days of inappropriate and unnecessary antifungals
  - Single center in England showed savings of > $280,000 (~£180,000) in first year

Clin Infect Dis 2015; 69: 361-392.
J Antimicrob Chemother 2014; 69: 1993-1999.

CANDIDIASIS

Patient Case #1

- IC is a 44 y/o male, transferred from OSH for abdominal pain and found to have necrotic bowel 2/2 ingestion of cocaine
  - Partial colectomy performed on admit
  - SCr on admit is 11, requiring CRRT
- VS (ICU day 6):
  - HR 115
  - RR 24
  - Tmax 101.5ºF
- Current antimicrobials:
  - Ceftazidime
  - Metronidazole
  - Vancomycin

Patient Case #1

- Patient has had low blood pressures since admit, currently being maintained on norepinepherine drip
- Team would like to start empiric antifungal therapy

Empiric Antifungal Therapy

- Low hanging fruit
  - Febrile neutropenic patients with persistent fever after 72-96 hours of broad spectrum antibiotics
- What about non-neutropenic patients?

Candida Risk Score

Population (n=1,669)	Multicenter prospective observational cohort study of adult patients admitted to the ICU for at least 7 days.
Intervention	Data were collected for all patients that met inclusion criteria Weekly samples were taken to determine colonization of the gastrointestinal, genitourinary or respiratory tracts

Table 4. Calculation of the Candida score: Variables selected in the logistic regression model

Variable	Coefficient (β)	Standard Error	Wald χ^2	*p* Value
Multifocal *Candida* species colonization	1.112	.379	8.625	.003
Surgery on ICU admission	.997	.319	9.761	.002
Severe sepsis	2.038	.314	42.614	.000
Total parenteral nutrition	.908	.389	5.851	.030
Constant	−4.916	.485	102.732	.000

ICU, intensive care unit.

Candida score = .908 × (total parenteral nutrition) + .997 × (surgery) + 1.112 (multifocal *Candida* species colonization) + 2.038 (severe sepsis). Candida score (rounded) = 1 × (total parenteral nutrition) + 1 × (surgery) + 1 (multifocal *Candida* species colonization) + 2 × (severe sepsis). All variables coded as follows: absent, 0; present, 1.

Crit Care Med 2006; 34: 730-737.

Candida Risk Score

B

Cutoff value	Sensitivity	False positive
1.055	.983	.653
1.509	.949	.485
1.963	.898	.426
2.069	.831	.312
2.074	.814	.301
2.526	.814	.259
2.982	.780	.251
3.026	.610	.132
3.093	.593	.130
3.547	.525	.092
4.001	.492	.077

- Determined that a score >2.5 can help to select for patients who may benefit from early antifungal therapy

Crit Care Med 2006; 34: 730-737.

Validation of the Candida Risk Score

Population	Patients admitted to ICU and exhibited signs of hospital-acquired severe sepsis or septic shock (n=94)	Admitted to ICU for sepsis (n=95)
Rate of candidiasis	5.3%	16.8%
Cutoff used	>3	≥3
PPV	23.8%	27.3%
NPV	100%	98.7%

- Very good negative predictor
- Candida risk score can help to identify patients at risk for invasive candidiasis but should be considered in the clinical context of the patient

Critical Care 2011; 15: R249.
Ann Intensive Care 2011;1:50

Patient Case

- What is IC's Candida Score?
  - A. 1
  - B. 2
  - C. 3
  - D. 4

Patient Case #1

- IC is a 44 y/o male, transferred from OSH for abdominal pain and found to have necrotic bowel 2/2 ingestion of cocaine
  - Partial colectomy performed on admit to BIDMC
- SCr on admit is 11, requiring CRRT
- VS (ICU day 6):
  - HR 115
  - RR 24
  - Tmax 101.5°F
- Patient has had low blood pressures since admit, currently being maintained on norepinepherine drip
- Current antimicrobials:
  - Ceftazidime
  - Metronidazole
  - Vancomycin

Patient Case #1

- IC is a 44 y/o male, transferred from OSH for abdominal pain and found to have necrotic bowel 2/2 ingestion of cocaine
  - Partial colectomy performed on admit to BIDMC
- SCr on admit is 11, requiring CRRT **Surgery +1**
- VS (ICU day 6):
  - HR 115
  - RR 24
  - Tmax 101.5°F
- Patient has had low blood pressures since admit, currently being maintained on norepinepherine drip
- Current antimicrobials:
  - Ceftazidime **Septic Shock +2**
  - Metronidazole
  - Vancomycin

(1,3)-β-D-glucan

- Multiple studies have shown widely variable data on the usefulness of this clinical test
- Detects part of fungal cell wall in *Candida* spp. and *Aspergillus* spp.
- Large multicenter trial with 163 patients with proven or probable IFI showed the following:

Table 3. Performance of the (1→3)-β-D-glucan (BG) assay for

BG cutoff value, pg/mL	Sensitivity, %	Specificity, %	Positive predictive value, %	Negative predictive value, %
80	64.4	92.4	80.0	73.0

Clin Infect Dis 2005;41:654-659

(1,3)-β-D-glucan- False positives

- Many factors have been proposed to cause false positive (1,3)-β-D-glucan tests
  - *Pneumocystis jiroveci* pneumonia (PJP)
  - Bacteremia
  - IVIg
  - Certain antibiotics
  - Hemodialysis with cellulose membranes
  - Certain wound care items

Candidemia: Risk Factors

- Central venous catheters
- Prolonged length of stay
- Renal failure
- Hemodialysis
- Parenteral nutrition
- Transplantation
- Immunosuppression
- Surgery
  - Especially abdominal surgery
- Broad spectrum antibiotics

Crit Care Med 2006; 34: 857-863.

Patient Case #1

- IC has a Candida Risk Score of 3 and multiple risk factors that have been associated with Candida infection in ICU patients
- Beta-D-Glucan is still pending
- Would you start antifungal therapy?
- What agent would you choose?

Diagnosis

- Yeast is a very uncommon cause of respiratory infection
- Yeast is a common urinary colonizer
  - First line treatment- take out urinary catheter
- No matter the quantity, yeast from blood is not a contaminant

Clin Infect Dis 2009; 48: 503-535.

Candidemia: Treatment

Host/disease factors	Recommended therapy
Immunocompetent **AND** azole naïve within 30 days **AND** hemodynamically stable **AND** no recent history of *C. krusei* or *C. glabrata*	**Fluconazole** 800 mg x 1, then 400 mg IV daily
Immunocompromised **OR** azole experienced within 30 days **OR** hemodynamically unstable **OR** recent history of *C. krusei* or *C. glabrata*	**Micafungin** 100 mg IV Daily OR Liposomal Amphotericin B 3mg/kg daily OR Voriconazole 6mg/kg q12h, then 3mg/kg q12h

Clin Infect Dis 2009; 48: 503-535.

Patient Case

- What agent would be the most appropriate to start in IC?
  - A. No therapy at this time
  - B. Fluconazole 800mg x1 then 400mg daily
  - C. Caspofungin 70mg x1 then 50mg daily
  - D. Liposomal amphotericin B 3mg/kg daily

Fluconazole vs. Anidulafungin for Invasive Candidemia

Population (n=245)	Patients >16 y/o with *Candida* spp recovered from a normally sterile site within 96 hours of enrollment and had signs/symptoms of infection or radiological evidence
Exclusion	• *C. kruseii* infection • Refractory Candida infection • >1 week of azole therapy in past 30 days • >48h of antifungal therapy • Osteomyelitis, endocarditis or meningitis
Intervention	Patients were randomly assigned to receive either fluconazole or anidulafungin therapy and were stratified based on APACHE II score and neutrophil count
Treatment response	Anidulafungin had higher rates of response at the end of IV therapy was found to be non-inferior No difference in 28-day mortality
Conclusions	Echinocandins and fluconazole appear to be equally effective in this population (non-neutropenic patients with APACHE <20)

N Engl J Med 2007; 356: 2472-2482.

Fluconazole vs. echinocandins for *C. glabrata* fungemia

Population (n=224)	Retrospective multicenter study of patients receiving fluconazole or an echinocandin for the treatment of *C. glabrata* candidemia
Exclusion	• Concomitant bacteremia • >48h of antifungal therapy before first positive result
Complete response at day 14	No significant difference in response at day 14 (p=0.383) There was a trend towards decreased response when comparing patients treated with fluconazole with more severe illness
Survival	No difference in mortality at any point (28 day; p=0.944)
Conclusions	Even in the case of *C glabrata*, patients treated with fluconazole who are clinically stable have similar rates of cure and no difference in mortality when compared to echinocandin therapy

J Antimicrob Chemother 2013; 68: 922-926

Patient case #1

- IC was started on fluconazole 400mg daily (with an 800mg load)
- On day 14 yeast from blood culture is speciated to *C. glabrata*
- Still no susceptibilities
- How would this change your current management of this patient?

Patient Case

- IC is clinically improving on fluconazole and is now out of the ICU, however cultures are growing *C. glabrata.*
- What is the best course of action?
  A. Continue fluconazole 400mg daily
  B. Increase fluconazole to 800mg daily
  C. Switch to micafungin 100mg daily
  D. Switch to liposomal amphotericin 3 mg/kg

Candidemia: Other Considerations

- Endocarditis should be a concern in all patients with candidemia
  - TTE or TEE should be obtained in patients with clinical suspicion for endocarditis
- Central lines should be removed, if possible, as *Candida* spp. may form biofilms
- All patients should receive an ophthalmology exam at least once

Clin Infect Dis 2009; 48: 503-535.

Candidal Endocarditis

- Few studies looking at treatment of patients with candidal endocarditis
- Treatment of choice is amphotericin B +/- flucytosine
- However, a small study suggests that echinocandins may have a role
  - All cause mortality of patients treated with caspofungin similar to those treated with amphotericin B in a chart review
- In vitro data suggests that amphotericin B and echinocandins have better penetration into biofilms

Eur J Clin Microbiol Infect Dis 2008; 27: 519-529.

INVASIVE ASPERGILLOSIS

Patient Case

- AG is a 65 year old male admitted for CSF relapse of AML, currently being treated with IT cytarabine
  - Multiple cycles
- On hospital day 30 he develops a fever to 102.3°F
- Currently has WBC count of 1.2, neutrophils are 35%
- Started on cefepime

Patient Case

- On day 3 of treatment with cefepime, patient continues to be febrile
- CT notes nodules in the lungs surrounded by ground glass opacities
- What diagnostic tests could help you determine the best treatment?

Patient Case

- At this point, based on consensus definitions what level of certainty do we have that AG has Aspergillosis?
  A. Possible
  B. Probable
  C. Proven

Aspergillus spp.

- Aspergillus spp. are molds that are ubiquitous worldwide
- Important cause of morbidity and mortality in immunocompromised patients
- Invasive infections most commonly occur in the lungs
- Most common species is *Aspergillus fumigatus*
  - May change based on location

Clin Infect Dis 2008; 46: 327-360.

Pulmonary Aspergillosis: Risk Factors

- Prolonged neutropenia
- Advanced HIV
- Inherited immunodeficiency syndrome
- Hematopoietic stem cell transplantation
- Lung transplantation

Clin Infect Dis 2008; 46: 327-360.

Pulmonary Aspergillosis: Signs and symptoms

- Nodules with halo sign on CT
- Positive fungal markers
  - Galactomannan
  - β-D-Glucan
- Cultures obtained via BAL, needle aspiration or thorascopic biopsy

Clin Infect Dis 2008; 46: 327-360.

Pulmonary Aspergillosis: Diagnosis

Consensus Definition for Invasive Fungal Disease	
Proven	Recovery of Aspergillus spp. from a normally sterile site with evidence of tissue damage or clinical correlation with infectious process at that site --Excludes BAL and sinus cavity specimen
Probable	Combination of host factors, clinical criteria and mycological evidence 1) Host is immunosuppressed 2) Pulmonary infection: CT with dense lesions, air crescent signs or cavitary lesions 3) Positive galactomannan or recovery of *Aspergillus* spp. from respiratory cultures
Possible	Combination of host factors and clinical criteria WITHOUT mycological evidence

Clin Infect Dis 2008; 46: 1813-1821.

Galactomannan Assay

- Galactomannan is a cell wall component of *Aspergillus* spp.
  - Released during invasive infection
- Large meta-analysis showed sensitivity of 71% and specificity of 89%
  - Better negative predictor than positive predictor
- False positives have been reported in patients receiving concurrent piperacillin-tazobactam therapy

Blood 2001; 97: 1604-1610.
Clin Infect Dise 2006; 42: 1417-1422.

Patient Case

- What test would move our certainty of *Aspergillus* spp. infection from possible to probable?
  A. β-(1,3)-D-glucan assay
  B. Galactomannan assay
  C. Sputum culture with yeast
  D. Repeat CT to confirm halo

Pulmonary Aspergillosis: Treatment

- Voriconazole is the treatment of choice
  - 6mg/kg q12 for 2 doses, then 4mg/kg
- Amphotericin B may also be effective
  - Amphotericin B deoxycholate dosed 1mg/kg daily
  - Lipid formulations better tolerated
    - Liposomal amphotericin B dosed 3-5 mg/kg/day
  - *A. terreus* is intrinsically resistant to amphotericin

Clin Infect Dis 2008; 46: 327-360.

Voriconazole vs. D-AMB for invasive aspergillosis

Population (n=277)	Randomized open label study of patients with probable or definite invasive aspergillosis and were immunocompromised. Mostly with lung involvement only and hematologic cancers.
Exclusion	Received 96 hours of therapy with amphotericin B or itraconazole, received interacting medications had LFTs >5x ULN, or were on mechanical ventilation.
Intervention	Randomized to receive amphotericin B deoxycholate 1-1.5mg/kg daily **OR** Voriconazole 6mg/kg q12h for two doses then 4mg/kg q12h
Response at week 12	Complete or partial response was 52.8% in voriconazole group and 31.6% in the amphotericin group (CI: 10.4-32.9)
Survival at week 12	Survival in voriconazole group was 70.8% and 57.9% in the amphotericin B group (CI: 0.4-0.88)
Conclusion	Voriconazole was found to have superior outcomes with respect to amphotericin B deoxycholate. Additionally voriconazole was better tolerated but had higher rates of visual disturbances.

N Engl J Med 2002; 347: 408-415

Combination Therapy

Population (n=454)	Randomized double blind placebo controlled trial of combination therapy in proven or probable invasive aspergillosis. Patients had to be >16 years of age
Exclusion	Progressive hematologic malignancies not likely to response to treatment, life expectancy <30 days, **mechanical ventilation**, >96 hours of antifungals before enrollment, pregnant or lactating, severe liver dysfunction
Intervention	Randomized to receive voriconazole 6 mg/kg q12 x2 doses then 4mg/kg BID for a total of 6 weeks of treatment (could switch to PO after 7 days) **OR** Voriconazole 6mg/kg q12h for two doses then 4mg/kg q12h PLUS anidulafungin 200mg x1 then 100mg daily for 2-4 weeks
Mortality at week 6 (mITT)	Mortality in combination therapy was 19.5% vs 27.8% in the monotherapy group (Difference -8.3% CI: -19 to 1.5, p=0.086)
Conclusion	Combination of voriconazole with anidulafungin resulted in a decrease in mortality in the mITT group, however this was not statistically significant. Multivariate analyses identified initial galactomannan level as being predictive of mortality.

Ann Intern Med 2015; 162: 81-89.

Isavuconazole in Aspergillosis

- Studies have not yet been published
- Randomized double blind study of patients with possible, probable or proven infection (n=231)
- No differences noted in 6 week all cause mortality or overall response at end of treatment
- Less ADEs in patients on isavuconazole,
  - No difference in serious ADEs or ADEs leading to d/c

Abstract 1211, Idweek 2014, IDSA
Ann Intern Med 2015; 162: 81-89.

Salvage Therapy

- Other agents have been studied in salvage therapy
  - Posaconazole 200mg QID
  - Caspofungin 70mg once then 50mg daily
  - Micafungin 100mg daily

Clin Infect Dis 2008; 46: 327-360.

Patient Case

- The team would like to know which medication to start for the treatment of AG's suspected Aspergilosis. What is the best option?
  A. Caspofungin
  B. Liposomal amphotericin B
  C. Voriconazole
  D. Posaconazole

Patient Case

- AG is started on voriconazole per your recommendations. What is the most clinically relevant interaction with AG's medications?
  A. Cefepime
  B. Prochlorperazine
  C. Citalopram
  D. Diphenoxylate/atropine

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