

Managing Fungal Sepsis Post-transplant

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MASSACHUSETTS
GENERAL HOSPITAL

TRANSPLANT CENTER

Candida
Cryptococcus
Aspergillus
Agents of mucormycosis
Comments on “others”

Clinical syndrome
Diagnostics
Treatment
Prophylaxis



The epidemiology and outcomes of invasive *Candida* infections among organ transplant recipients in the United States: results of the Transplant-Associated Infection Surveillance Network (TRANSNET)

Transplant Infectious Disease 2016; 18: 921–931

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Lisa Brumble⁴ | Allison Freifeld⁵ | Susan Hadley⁶ | Loreen Herwaldt⁷ |
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The TRANSNET Investigators

- 15 USA transplant centers, 2001 through 2006
- A total of 639 cases of IC (533 proven, 106 probable) occurred in 594 OTRs from almost 17 000 patients. The most common site of IC was bloodstream in 44% of cases, followed by intra-abdominal infection (14%)
- Median time to onset was 80 days after transplant

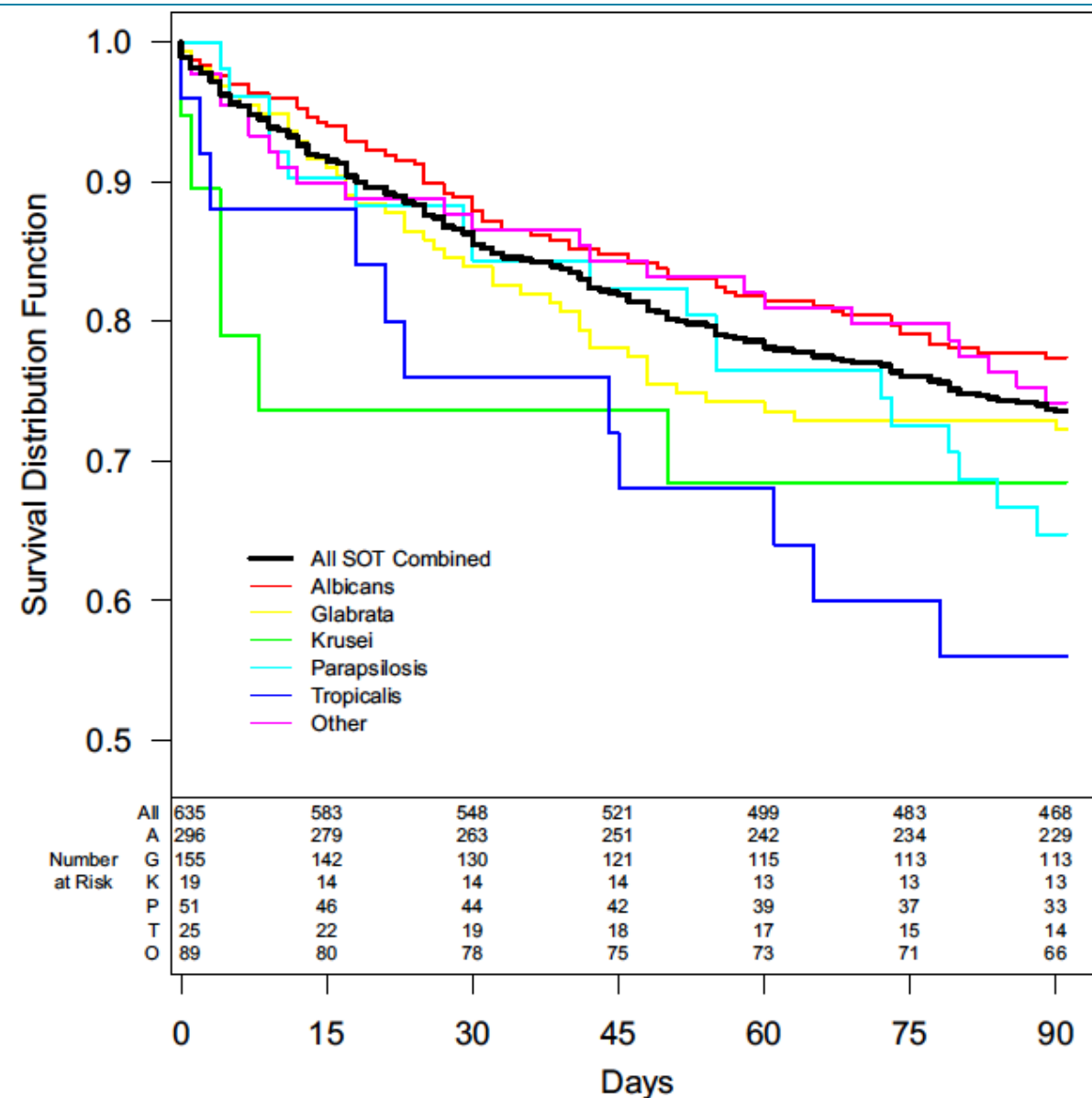


FIGURE 1 Kaplan–Meier probability of survival in solid organ transplant (SOT) recipients according to *Candida* species

Candidemia: there are three major routes by which *Candida* gain access to the bloodstream

- Gastrointestinal tract mucosal barrier breakdown (translocation)
- Via an intravascular catheter
- From a localized focus of infection, such as surgical site, pyelonephritis

Sterile space infection

- Surgical site (abdomen, thorax)
- Blood

Non-sterile space infection

- Mouth/esophagus
- Urine*

Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the Infectious Diseases Society of America

Peter G. Pappas,¹ Carol A. Kauffman,² David R. Andes,³ Cornelius J. Clancy,⁴ Kieren A. Marr,⁵ Luis Ostrosky-Zeichner,⁶ Annette C. Reboli,⁷ Mindy G. Schuster,⁸ Jose A. Vazquez,⁹ Thomas J. Walsh,¹⁰ Theoklis E. Zaoutis,¹¹ and Jack D. Sobel¹²

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It is important to realize that guidelines cannot always account for individual variation among patients. They are not intended to supplant physician judgment with respect to particular patients or special clinical situations. IDSA considers adherence to these guidelines to be voluntary, with the ultimate determination regarding their application to be made by the physician in the light of each patient's individual circumstances.

Candida auris: a Novel Addition

Phenotypically resembles *Candida haemulonii*; requires use of molecular methods for identification

Can be a challenge to identify and treat, especially in resource limited settings, where molecular identification may not be immediately available and access to antifungals other than fluconazole may be limited

Highly resistant: Using stringent break points, 93% of isolates were resistant to fluconazole, 35% to amphotericin B, and 7% to echinocandins; 41% were resistant to 2 antifungal classes and 4% were resistant to 3 classes (Lockhart et al, CID 2017:64)

Enhanced ability to colonize patients perhaps indefinitely and persist in the healthcare environment, thus can spread between patients in healthcare settings

CID 2017:64 (15 January)

Simultaneous Emergence of Multidrug-Resistant *Candida auris* on 3 Continents Confirmed by Whole-Genome Sequencing and Epidemiological Analyses

Shawn R. Lockhart,¹ Kizee A. Etienne,¹ Snigdha Vallabhaneni,¹ Joveria Farooqi,⁴ Anuradha Chowdhary,⁵ Nelesh P. Govender,⁷ Arnaldo Lopes Colombo,⁸ Belinda Calvo,⁹ Christina A. Cuomo,² Christopher A. Desjardins,² Elizabeth L. Berkow,¹ Mariana Castanheira,³ Rindidzani E. Magobo,⁷ Kauser Jabeen,⁴ Rana J. Asghar,⁵ Jacques F. Meis,^{10,11} Brendan Jackson,⁵ Tom Chiller,¹ and Anastasia P. Litvinseva¹

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Table 2. Antifungal Susceptibility Data for 54 *Candida auris* Isolates

Antifungal	MIC Range, µg/mL	MIC ₅₀ , µg/mL	MIC ₉₀ , µg/mL
Fluconazole	4–256	128	256
Voriconazole	0.03–16	2	8
Itraconazole	0.125–2	0.5	1
Posaconazole	0.06–1	0.5	1
Caspofungin	0.03–16	0.25	1
Anidulafungin	0.125–16	0.5	1
Micafungin	0.06–4	0.25	2
Flucytosine	0.125–128	0.125	0.5
Amphotericin B	0.38–4	1	2

Abbreviations: MIC, minimum inhibitory concentration; MIC₅₀, MIC for 50% of isolates; MIC₉₀, MIC for 90% of isolates.

Candida auris in South Africa, 2012–2016

Nelesh P. Govender, Rindidzani E. Magobo, Ruth Mpembe, Mabatho Mhlana, Phelly Matlapeng, Craig Corcoran, Chetna Govind, Warren Lowman, Marthinus Senekal, Juno Thomas

Emerging Infectious Diseases • www.cdc.gov/eid • Vol. 24, No. 11, November 2018

Characteristic	Cases with available data, n = 1,579	Invasive disease, n = 451	Colonization, n = 1,128
Median patient age, y (interquartile range)†	n = 1,576	55 (41–68)	63 (49–74)
Patient sex, no. (%)	n = 1,540	n = 442	n = 1,098
M	957 (62)	273 (62)	684 (62)
F	583 (38)	169 (38)	414 (38)
Health sector, no. (%)	n = 1,549	n = 439	n = 1,110
Private	1,435 (93)	325 (74)	1,110 (100)
Public	114 (7)	114 (26)	0
Province, no. (%)	n = 1,465	n = 424	n = 1,041
Gauteng	1,336 (91)	380 (90)	956 (92)
Mpumalanga	72 (5)	25 (6)	47 (5)
North West	20 (1)	7 (2)	13 (1)
Other provinces	37 (3)	12 (2)	25 (2)

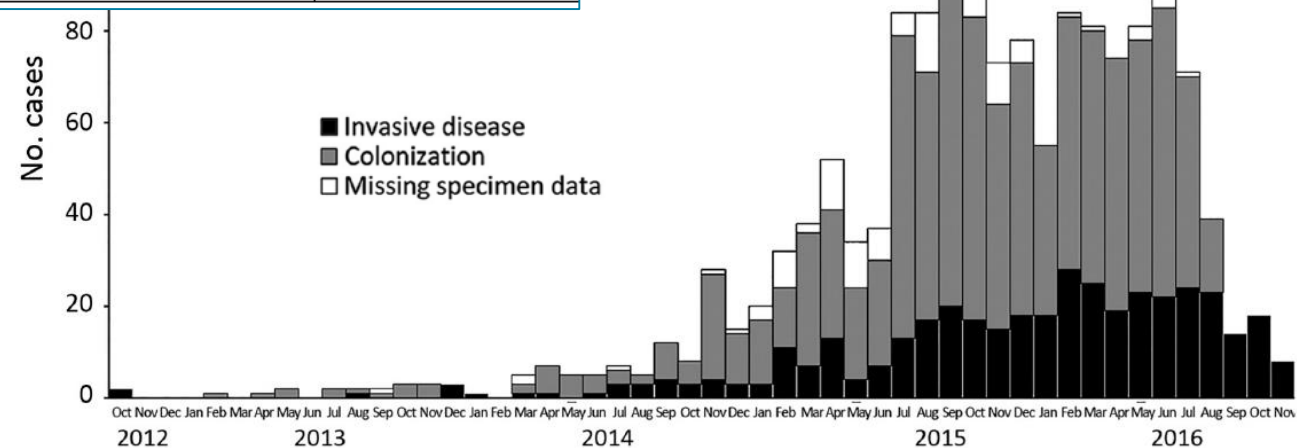


Figure 2. Distribution of cases of *Candida auris* by type of infection and date of specimen collection, South Africa, 2012–2016. n = 1,306.

Blood cultures: overall sensitivity for invasive candidiasis is ~ 50% (Clancy CID 2013)

Can be confounded by:

Intermittent/nonpersistent candidemia

Deep-seated candidiasis that persists after sterilization of the bloodstream

Deep-seated candidiasis resulting from direct inoculation of Candida w/o candidemia

Cultures of tissues or fluid from infected sterile sites also have poor sensitivity (often <50%)

With slow turnaround times, and requirement for invasive sampling procedures

Cultures of non-sterile sites

Can be very confounding; need careful clinical review to determine if positive results represent colonization versus infection

Goal is to shorten the time to diagnosis of invasive candidiasis and initiation of antifungal therapy

1,3 beta D glucan (cell wall constituent of Candida species, Aspergillus species, Pneumocystis jiroveci, and several other fungi) – approved by the FDA as an adjunct to cultures for the diagnosis of invasive fungal infections; assay has poor sensitivity/specificity (~80% each)

BDG when collected a mean of 2.5 days (range 1- 10 days) prior to blood culture collection were positive (Chibabhai V et al, Comparative sensitivity of 1,3 beta-D-glucan for common causes of candidaemia in South Africa. Mycoses. Aug 2019)

Candida PCR /T2 magnetic resonance - lack of standardized methodologies and multicenter validation of assay performance

“A combination of tests, or a single test at multiple time points, may be preferable to relying on one test at a single time point.” (McKeating et al, J Clin Path 2018 May;71(5):420-424)

Date	Group	Type	Tests	Results																			
04/10/2019 06:30	BLOOD/SERUM	BLOOD	BLOOD CULTURE	Aerobic bottle: CANDIDA KRUSEI RESULT CALLED TO CARE UNIT AND/OR MD ON 04/11/19 Anaerobic bottle: NO GROWTH																			
04/08/2019 09:49	BLOOD/SERUM	BLOOD	BLOOD CULTURE	Aerobic bottle: CANDIDA KRUSEI SEE EARLIER CULTURE FOR SENSITIVITIES RESULT CALLED TO CARE UNIT AND/OR MD 4/9/19 Anaerobic bottle: NO GROWTH																			
04/08/2019 09:49	<table><tr><td></td><td>4/6/2019 0945</td><td>2/26/2019 0452</td><td>2/19/2019 0440</td><td>2/12/2019 1730</td><td>2/5/2019 1258</td></tr><tr><td>INFECTIONOUS DISEASE...</td><td></td><td></td><td></td><td></td><td></td></tr><tr><td>1-3 Beta Glucan</td><td><31</td><td><31</td><td><31</td><td><31</td><td><31</td></tr></table>						4/6/2019 0945	2/26/2019 0452	2/19/2019 0440	2/12/2019 1730	2/5/2019 1258	INFECTIONOUS DISEASE...						1-3 Beta Glucan	<31	<31	<31	<31	<31
		4/6/2019 0945	2/26/2019 0452	2/19/2019 0440	2/12/2019 1730	2/5/2019 1258																	
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1-3 Beta Glucan	<31	<31	<31	<31	<31																		
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04/08/2019 00:56	BLOOD/SERUM	BLOOD	BLOOD CULTURE	Aerobic bottle: CANDIDA KRUSEI SEE EARLIER CULTURE FOR SENSITIVITIES RESULT CALLED TO CARE UNIT AND/OR MD 4/9/19 Anaerobic bottle: NO GROWTH																			
04/06/2019 08:50	BLOOD/SERUM	BLOOD	BLOOD CULTURE	Aerobic bottle: CANDIDA KRUSEI RESULT CALLED TO CARE UNIT AND/OR MD ON 4/7/19 Anaerobic bottle: NO GROWTH																			

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SPECIAL ISSUE-TRANSPLANT INFECTIOUS DISEASES



Candida infections in solid organ transplantation: Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice

Saima Aslam¹ | Coleman Rotstein² | on behalf of the AST Infectious Disease Community of Practice

TABLE 1 General susceptibility patterns of Candida species

Species	Fluconazole	Itraconazole	Voriconazole	Posaconazole	Isavuconazole	5FC	AmB	Echinocandins
Candida albicans	S	S	S	S	S	S	S	S
Candida tropicalis	S	S	S	S	S	S	S	S
Candida parapsilosis	S	S	S	S	S	S	S	S to R ^a
Candida glabrata	S-DD to R	S-DD to R	S-DD to R	S-DD to R	S-DD to R	S	S to I	S to R
Candida krusei	R	S-DD to R	S	S	S	I to R	S to I	S
Candida lusitanae	S	S	S	S	S	S	S to R	S
Candida auris	R	R	R	R	-	S	S to R	S to R

all *C. krusei* isolates
are resistant to fluconazole

MASSACHUSETTS GENERAL HOSPITAL MICROBIOLOGY DEPARTMENT
ANTIMICROBIAL SUSCEPTIBILITY – JAN. - DEC. 2018

Yeast	No. of Strains	Fluconazole (% susceptible)
Candida albicans	341	94
Candida glabrata*	155	89
Candida parapsilosis	64	94
Candida tropicalis	32	88

Note: Candida krusei are intrinsically resistant to fluconazole.
* See “Antimicrobial Costs” table for information about the need for higher fluconazole dosing in *C. glabrata* infections.

2014 Yeast	No of Strains	Fluconazole (% susceptible)
Candida albicans	337	99
Candida glabrata*	154	78
Candida parapsilosis	67	96
Candida tropicalis	36	92

Initial empiric management: consider recent prophylaxis/exposures, type of infection (life-threatening versus not), drug interactions

If no recent azoles and not life threatening, probably fine to use azole

If suspect may be temporary use and want to avoid tacrolimus/mTor interactions, echinocandins (caspofungin/micafungin)

However, if recent azole exposure, prolonged hospital stay, or life threatening infection, +/- need to avoid drug interactions, consider echinocandins (caspofungin/micafungin) or amphotericin B/Ambisome

Tailor therapy as per culture data and antifungal susceptibility data, or based on literature

Severe, life-threatening or unrelenting infection, consider flucytosine (5FC)

For Candida, would rarely double cover, but consider for filamentous fungal infections (aspergillosis, mucormycosis)

C. auris “If the patient does not respond clinically to an echinocandin or has persistent candidemia for >5 days, the patient can be switched to a lipid formulation of amphotericin B 5 mg/kg IV daily.” (UpToDate)

Lines/catheters out, drain/wash out collections, ophthalmologic exam, repeat blood cultures, reduce immunosuppression (?)

XIV. What Is the Treatment for Urinary Tract Infections Due to *Candida* Species?

What Is the Treatment for Asymptomatic Candiduria?

Recommendations

97. Elimination of predisposing factors, such as indwelling bladder catheters, is recommended whenever feasible (*strong recommendation; low-quality evidence*).
98. Treatment with antifungal agents is NOT recommended unless the patient belongs to a group at high risk for dissemination; high-risk patients include neutropenic patients, very low-birth-weight infants (<1500 g), and patients who will undergo urologic manipulation (*strong recommendation; low-quality evidence*).
99. Neutropenic patients and very low-birth-weight infants should be treated as recommended for candidemia (see sections III and VII) (*strong recommendation; low-quality evidence*).
100. Patients undergoing urologic procedures should be treated with oral fluconazole, 400 mg (6 mg/kg) daily, OR AmB deoxycholate, 0.3–0.6 mg/kg daily, for several days before and after the procedure (*strong recommendation; low-quality evidence*).

What Is the Treatment for Symptomatic Candida Cystitis?

Recommendations

101. For fluconazole-susceptible organisms, oral fluconazole, 200 mg (3 mg/kg) daily for 2 weeks is recommended (*strong recommendation; moderate-quality evidence*).
102. For fluconazole-resistant *C. glabrata*, AmB deoxycholate, 0.3–0.6 mg/kg daily for 1–7 days OR oral flucytosine, 25 mg/kg 4 times daily for 7–10 days is recommended (*strong recommendation; low-quality evidence*).
103. For *C. krusei*, AmB deoxycholate, 0.3–0.6 mg/kg daily, for 1–7 days is recommended (*strong recommendation; low-quality evidence*).
104. Removal of an indwelling bladder catheter, if feasible, is strongly recommended (*strong recommendation; low-quality evidence*).
105. AmB deoxycholate bladder irrigation, 50 mg/L sterile water daily for 5 days, may be useful for treatment of cystitis due to fluconazole-resistant species, such as *C. glabrata* and *C. krusei* (*weak recommendation; low-quality evidence*).

Be aware that few antifungals reach the bladder!

Candida

Cryptococcus

Aspergillus

Agents of mucormycosis

Comments on “others”

Clinical syndrome

Diagnostics

Treatment

Prophylaxis

Clinical Vignette

Middle aged man presents 5 years after kidney transplant w/ slowly progressive headache, anorexia, balance disturbance and lack of focus; had been visiting daughter who had many pigeons in her yard

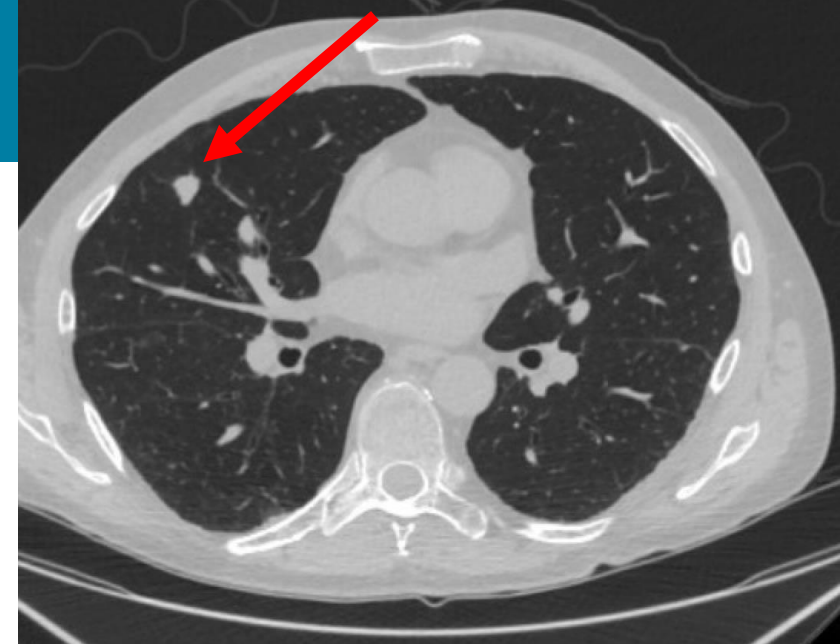
CSF: +cryptococcal antigen 1:1024

Blood +cryptococcal antigen 1:8192

AmbiSome 5mg/kg and 5FC x 3 weeks then isavuconazole

CRYPTOCOCCUS NEOFORMANS SUSCEPTIBILITY @ UNIVERSITY OF TEXAS HEALTH SCIENCE CENTER

Antibiotic	MIC Result
Amphotericin B	0.5
Fluconazole	8 🤖
Flucytosine	4
Isavuconazole	0.06
Posaconazole	0.25
Voriconazole	0.125



<https://medicine.academic.ru/pictures/medicine/383.jpg>

Induction	Duration
CNS disease, disseminated disease, or moderate-to-severe pulmonary disease	
Preferred therapy	
Liposomal amphotericin B 3-4 mg/kg/d or amphotericin B lipid complex 5 mg/kg/d plus 5-flucytosine 100 mg/kg/d ^a	Minimum of 2 wk
Alternative therapy	
Liposomal amphotericin B 3-4 mg/kg/d or amphotericin B lipid complex 5 mg/kg/d	Minimum of 4-6 wk
Consolidation	
Fluconazole 400-800 mg/d	8 wk
Maintenance	
Fluconazole 200-400 mg/d	Minimum of 6-12 mo
Pulmonary disease	
Asymptomatic or mild-to-moderate disease ^b	
Fluconazole 400 mg/d	6-12 mo
Severe pulmonary disease, or azole use not an option	
Same as for CNS disease	

8 | SUMMARY POINTS

- Serial lumbar punctures should be performed for the management of elevated ICP (strong, moderate)
- Temporary or permanent CSF drainage should be considered for in patients where serial lumbar punctures fail to normalize ICP (strong, low)
- Immune reconstitution syndrome can occur within weeks of start of antifungal therapy and reduced immunosuppression. Exclusion of clinical failure with repeat cultures is warranted before initiating corticosteroid treatment (weak, low)

Mystery Case



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68yo man s/p heart transplant Dec 2018

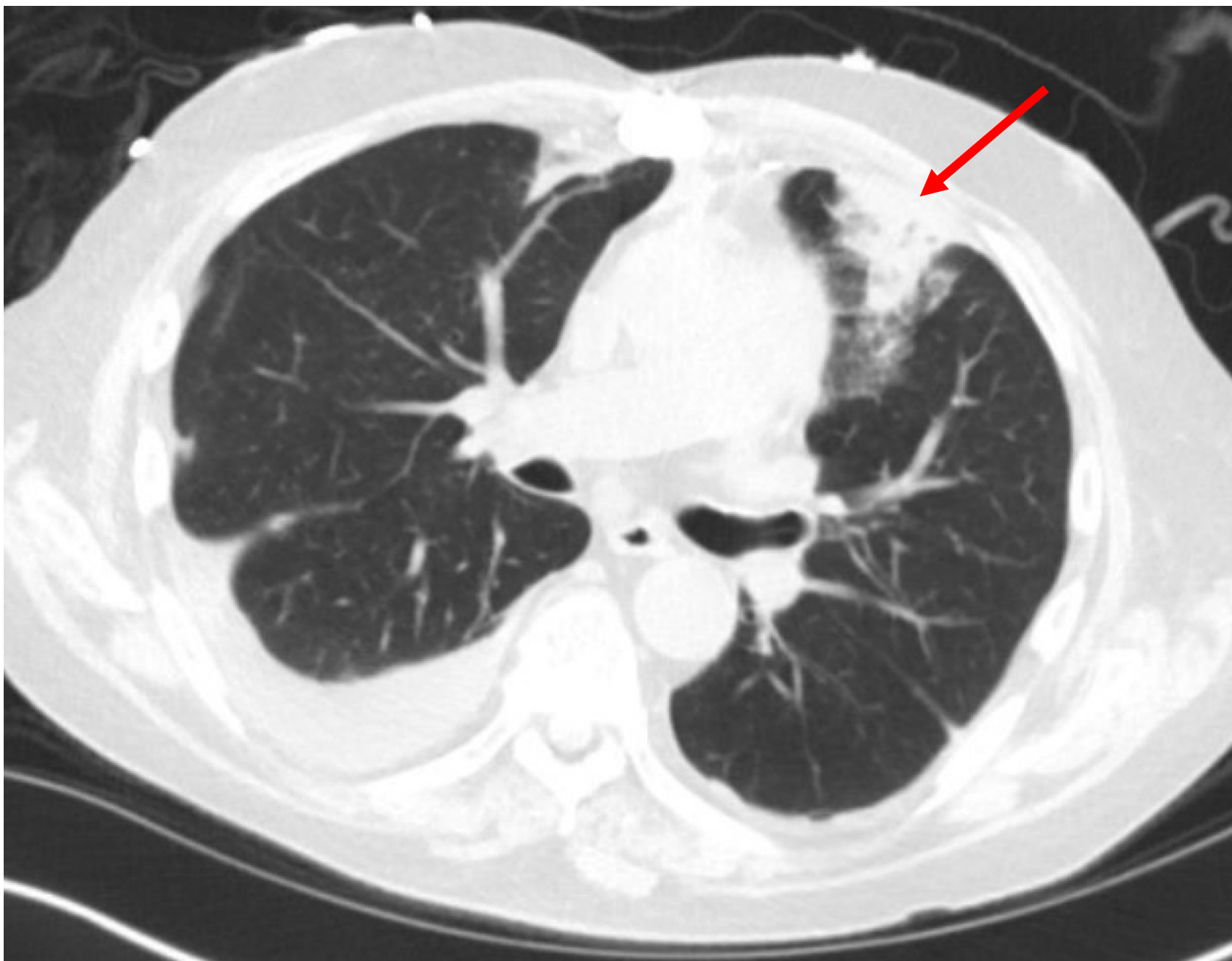
On valganciclovir/atovaquone (for pneumocystis/Toxoplasmosis)/nystatin swish & swallow

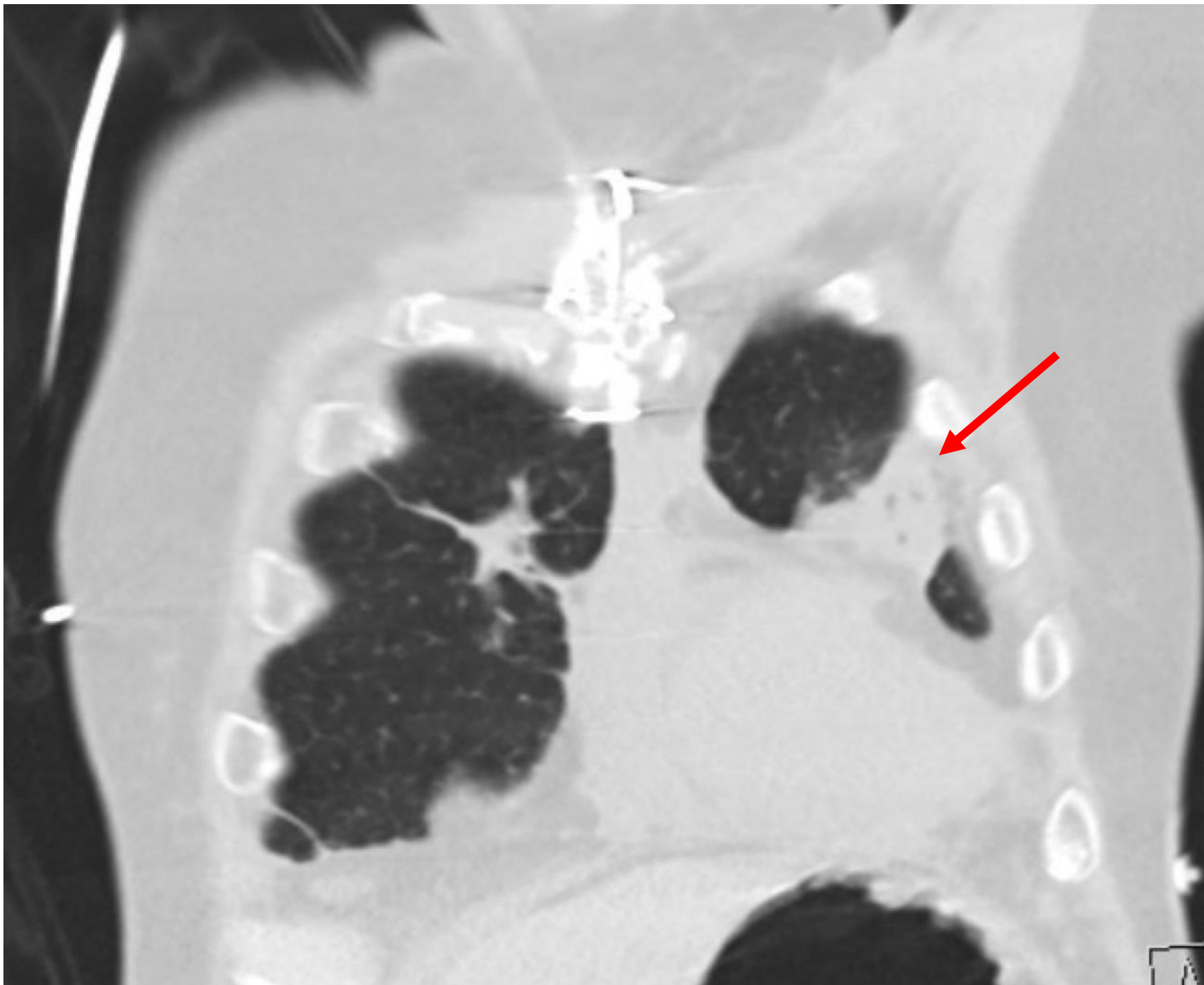
He had a low white blood cell count and his valganciclovir was stopped early. He has also suffered from pancytopenia.

Early May 2019 – develops active CMV viremia –started on treatment with valganciclovir 450 mg twice a day (dosed to lower GFR).

He had an Enterobacter bacteremia in May for which he received 2 weeks of treatment.

He then presented with pneumonia...





ASPERGILLUS FLAVUS

“He has invasive *Aspergillus flavus* for which he has been treated initially with AmBisome 5mg/kg followed by voriconazole 6mg/kg IV q 12 hours x 2 then 4 mg/kg PO q12 hours which was then therapeutic at a level of 3.3. As expected he has had significant drug interactions with his tacrolimus for which he has had high levels.”



ASPERGILLUS FLAVUS

(No CLSI interpretive guidelines available; MIC dilution method)

<u>Antibiotic</u>	<u>Result</u>
Amphotericin B	1
Isavuconazole	1
Itraconazole	0.5
Micafungin	≤ 0.015
Posaconazole	0.125
Voriconazole	1

Blood galactomannan antigen is >3.375 , 1,3 beta D glucan is >500

Invasive Aspergillosis in solid-organ transplant recipients: Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice

Shahid Husain¹  | Jose F. Camargo²  on behalf of the AST Infectious Diseases Community of Practice

Transplant type	Risk factor
Liver transplant recipients	
Early (0-3 mo)	<ul style="list-style-type: none">• Re-transplantation• Renal failure, particularly requiring renal replacement therapy• Fulminant hepatic failure• MELD > 30• Reoperation involving thoracic or intra-abdominal cavity
Late (>3 mo)	<ul style="list-style-type: none">• Cytomegalovirus infection• Creatinine > 3.3 g/dL
Lung transplant recipients	
	<ul style="list-style-type: none">• Single-lung transplant• Early airway ischemia• Cytomegalovirus infection• Rejection and augmented immunosuppression within last 3 mo, particularly in CF patients• Pre-transplant <i>Aspergillus</i> colonization• Post-transplant <i>Aspergillus</i> colonization within a year of transplant• Positive intraoperative <i>Aspergillus</i> culture in CF patients• Acquired hypogammaglobulinemia (IgG <400 mg/dL)
Heart transplant recipients	
	<ul style="list-style-type: none">• <i>Aspergillus</i> colonization• Airborne <i>Aspergillus</i> spores in ICU• Reoperation (thoracic)• CMV disease• Post-transplant hemodialysis• Existence of an episode of IA in the program 2 mo before or after heart transplant
Kidney transplant recipients	
	<ul style="list-style-type: none">• Pre-transplant diagnosis of COPD• Acute rejection episode in last 3 mo• Graft failure• High and prolonged duration of corticosteroids

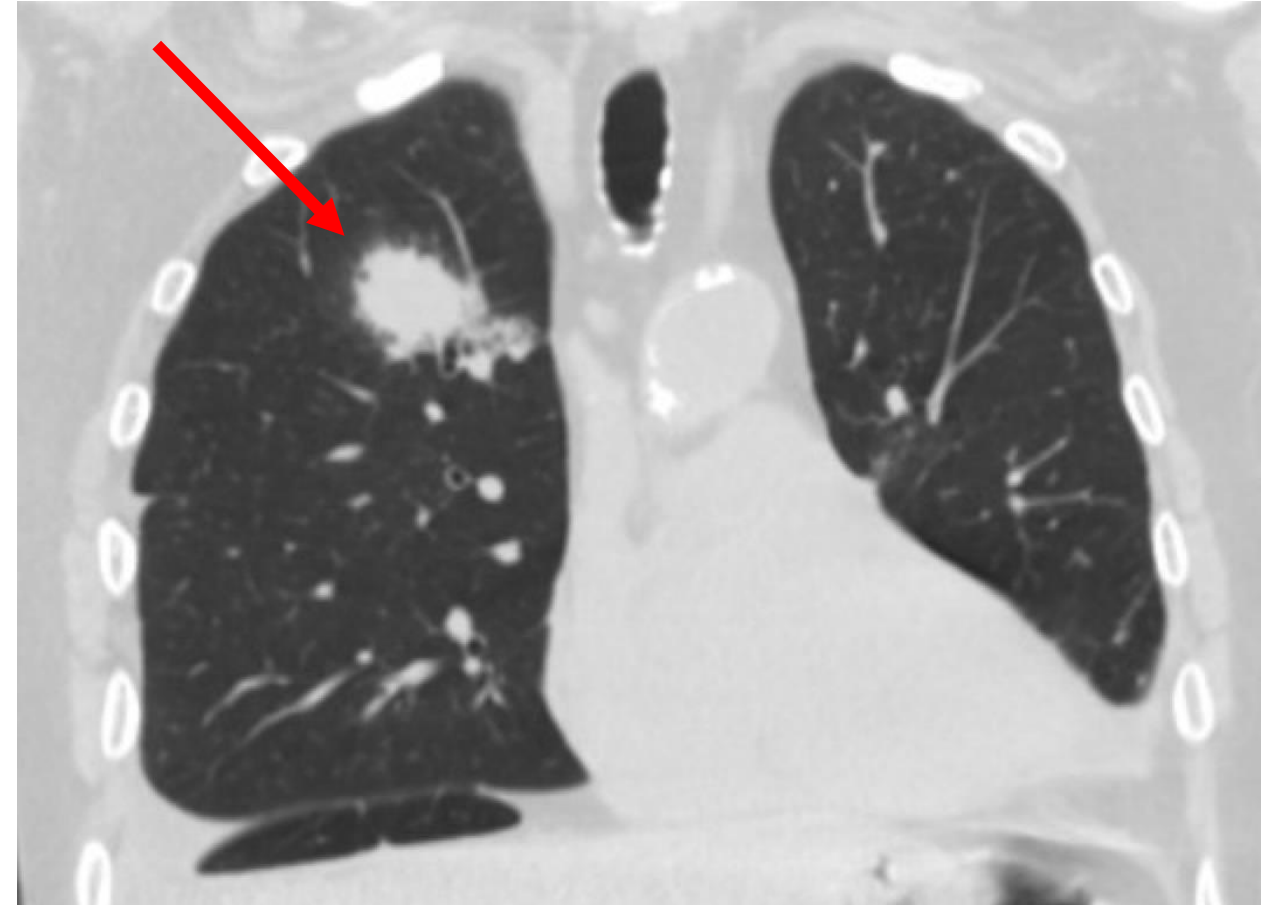
Invasive Aspergillosis in solid-organ transplant recipients:
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Infectious Diseases Community of Practice

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of Practice

TABLE 2 Antifungal therapy for IA in adult organ transplant recipients

Drug	Dosing (adult)	TDM	Comments
<i>Primary therapy</i>			
Voriconazole	6 mg/kg IV/PO ^a every 12 h for 1 d, followed by 4 mg/kg IV/PO every 12 h	Target trough level for treatment is >1 mg/L. ^{179,180,184} A level of 1-5.5 mg/L is considered adequate for most patients. A higher target (eg, 2-6 mg/L) should be used if there is disease with a poor prognosis (eg, CNS infection, bulky disease, multifocal infection); infections with pathogen with elevated MICs (eg, an MIC of 2 mg/L) ¹²⁸ Once steady-state levels have been reached, repeat sampling is warranted every 3-5 d ¹⁸⁴ in unstable patients and when there is uncertainty about voriconazole concentrations Measurement of serum trough concentration within 5-7 d	Due to accumulation of the IV vehicle (cyclodextrin), the manufacturer recommends the use of oral voriconazole in patients with CrCl <50 mL/min. In clinical practice, however, IV voriconazole has been safely administered to patients with different degrees of renal failure ^{209,210} Monitoring of hepatic function and CNI/mTOR inhibitor agent levels is recommended Non-linear (ie, highly variable) pharmacokinetics
<i>Alternative therapies</i>			
Isavuconazole	372 mg (isavuconazole 200 mg) IV/PO ^a every 8 h for 6 doses, followed by 372 mg (isavuconazole 200 mg) IV/PO once daily	Trough level in the range of 2-3 mg/L (mean concentration range from phase II/III clinical studies) after day 5 suggests adequate drug exposure ¹²⁸ No apparent relationship between exposure and efficacy to support routine TDM for isavuconazole ¹⁸³ Has 130-h half-life—long clearance after discontinuation	Monitoring of hepatic function and CNI/mTOR inhibitor agent levels is recommended Dose adjustment is not required in renal impairment Linear pharmacokinetics with low interpatient variability ¹³⁶
Liposomal amphotericin B (AmBisome [®])	3-5 mg/kg/d IV	There is currently insufficient evidence to support the routine use of TDM	Monitoring of electrolytes, and renal and hepatic function is recommended Higher dosages are not more effective Better tolerated than Abelcet [®]
Amphotericin B Lipid Complex (Abelcet [®])	5 mg/kg/d IV	There is currently insufficient evidence to support the routine use of TDM	Monitoring of electrolytes, and renal and hepatic function is recommended Higher dosages are not more effective

Routine clinic visit in a month ...



Repeat bronchoscopy shows...

GRAM STAIN: Abundant RED BLOOD CELLS , Moderate POLYS , Rare GRAM POSITIVE COCCI in PAIRS

**FUNGAL CULT/WET PREP:
WET PREP HYPHAE, NONSEPTATED, RESULT CALLED TO CARE UNIT AND/OR MD**

AFB SMEAR: NO ACID FAST BACILLI OBSERVED

Procedure(s): RIGHT UPPER LOBECTOMY, INTERCOSTAL MUSCLE FLAP OVER BRONCHIAL CLOSURE; EXTENSIVE PNEUMOLYSIS; BRONCHOSCOPY FLEXIBLE

“The flexible bronchoscope was introduced down the endotracheal tube...we then advanced down the right side where the right upper lobe had necrotic tissue within the segmental bronchi. The main bronchus of the right upper lobe appeared to be without necrotic tissue. The rest of the bronchus intermedius and lower middle lobes were widely patent with minimal secretions.... We made a standard posterior lateral thoracotomy ...We then began by affecting the chest where there were dense adhesions anteriorly likely from his previous sternotomy. This was a tedious and difficult dissection to take down these adhesions. With this pneumolysis taking over an hour we finally freed up the lung. His hilum was rather foreshortened and with significant inflammation... We noted there was significant congestion of the right upper lobe consistent with his underlying infectious process. Were able to identify the apical pulmonary artery branches. I surrounded these after a difficult and long tedious dissection and divided this with a vascular staple load. We then swept nodal tissue up around the bronchus. This was particularly inflamed. I was able to get around the bronchus and divided this with a thick tissue stapler. He had almost totally incomplete fissures. We were able to, with thick tissue staple loads, complete the fissure between the superior segment of the lower lobe in the upper lobe as well as to the middle lobe in the upper lobe. We then used the argon beam to coagulate right areas within the chest particularly anteriorly where we are taking down significant adhesions. ... We then brought the lung up, closed the chest in layers and the patient was awoken and extubated after leaving rib blocks.”

LUNG, RIGHT UPPER LOBE, LOBECTOMY:

Angioinvasive fungal bronchopneumonia.

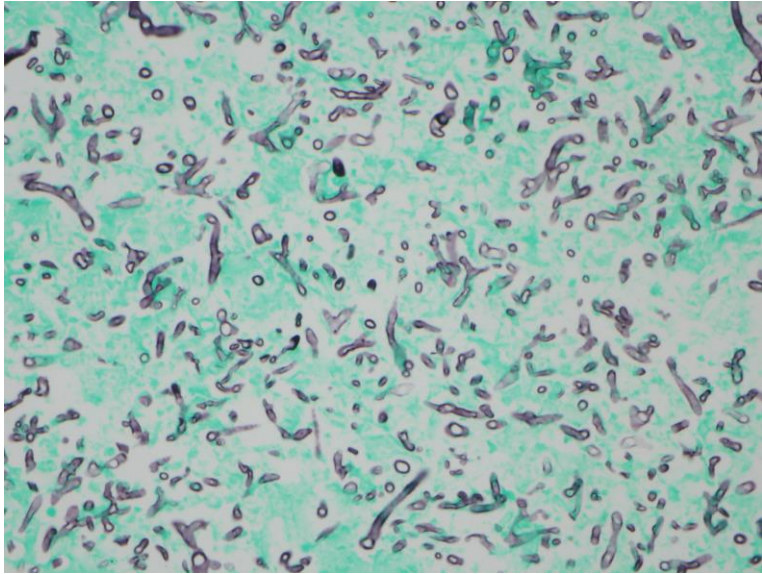
Fungal hyphae are present at the vascular margin and soft tissue adjacent to the bronchial margin.

Immunoreactivity for cytomegalovirus (CMV) in rare cells.

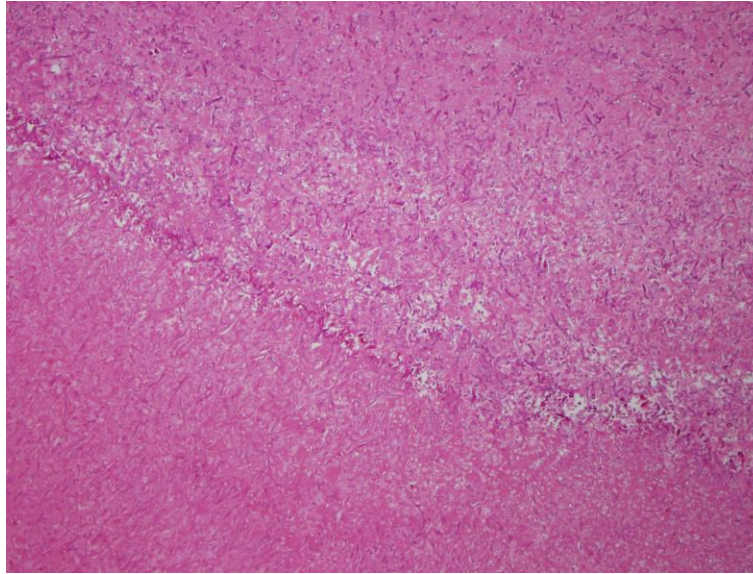
Note: Sections show abundant fungal hyphae, in some areas (such as block C1) with rare septation and ribbon-like morphology that are concerning for mucormycosis; however, other areas (such as block C9) show fungal hyphae with frequent septation and narrow angle branching, suggestive of *Aspergillus* spp. No yeast forms are seen. Background lung with multifocal acute fibrinous pneumonia, along with three (3) reactive lymph nodes. Immunostains for *Aspergillus* antigen show multifocal positivity. GMS, PAS, PAS-D, Brown-Hopps, AFB, and Steiner stains examined. No mycobacterial or bacterial microorganisms are seen. Elastic stains and immunostain for SMA highlight areas of fungal angioinvasion. Differential diagnosis includes zygomycetes, *aspergillus*, other fungal microorganisms, or a combination thereof. Correlation with microbiologic culture and molecular testing is advised.

Pathology Stains

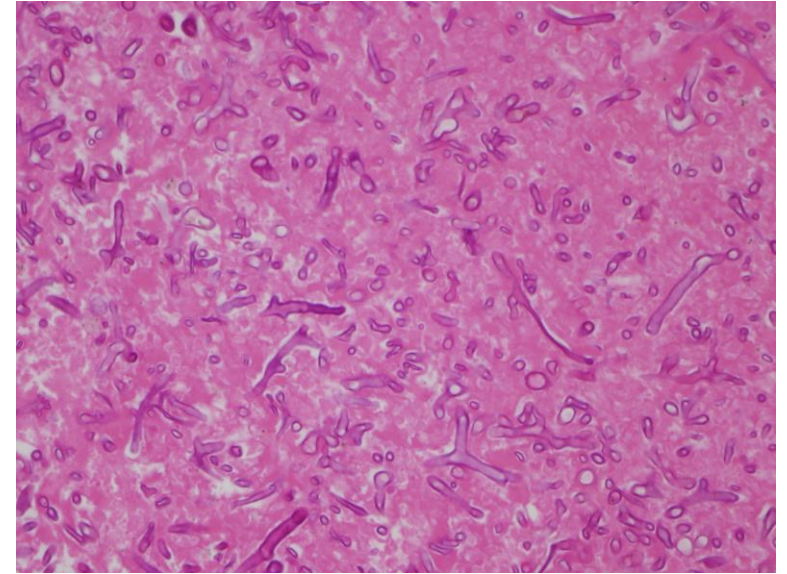
Mucor-like



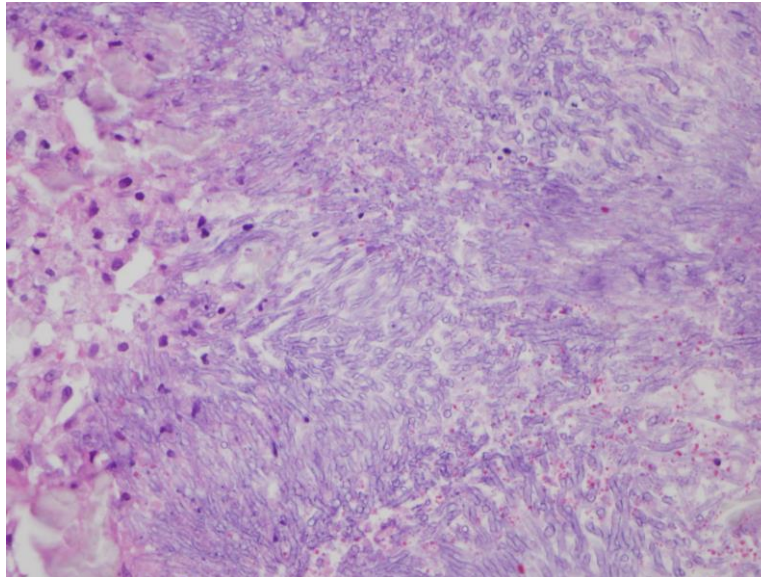
Grocott-Gömöri methenamine silver (GSM) 400x



Hematoxylin and eosin (H&E) stain 100x & 400X



Aspergillus-like



H&E stain 400X

Nothing sent to microbiology lab from surgery, alas

Rhizopus oryzae speciated via 18S rRNA sequencing at U Washington; no susceptibilities available

Plan for long term posaconazole; we assumed *Aspergillus flavus* from prior cultures

Surprise!!

NOCARDIA NOVA COMPLEX

- ♣ amikacin: Susceptible
- ♣ amoxicillin/clavulanate: Resistant
- ♣ ceftriaxone: Susceptible
- ♣ ciprofloxacin: Resistant
- ♣ clarithromycin: Susceptible ←
- ♣ doxycycline: Intermediate
- ♣ imipenem: Susceptible
- ♣ linezolid: Susceptible
- ♣ minocycline: Susceptible
- ♣ moxifloxacin: Susceptible ←
- ♣ tobramycin: Intermediate
- ♣ trimethoprim/sulfamethoxazole: Susceptible

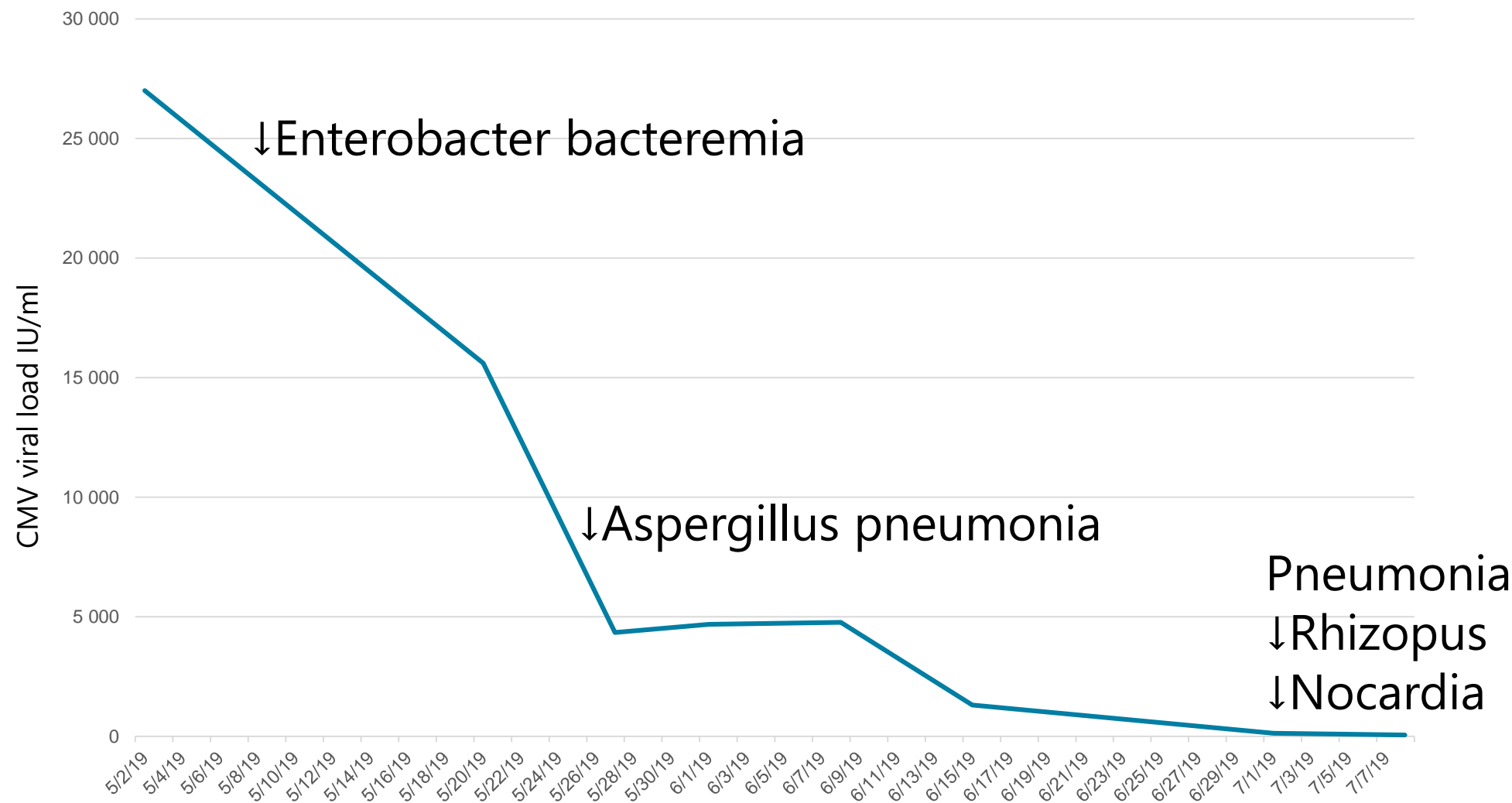
Emerging fungal infections in solid organ transplant recipients: Guidelines of the American Society of Transplantation Infectious Diseases Community of Practice

Shmuel Shoham¹ | Edward A. Dominguez² | on behalf of the AST Infectious Diseases Community of Practice

TABLE 2 Recommended treatment of emerging and rare fungal infections in solid organ transplant recipients

Fungal pathogen (references)	Initial therapy	Alternative therapy
Mucormycetes	<p>Surgical excision/debridement is recommended for all infections outside of lungs</p> <p>Induction therapy:</p> <ul style="list-style-type: none"> • LF-AmB is the treatment of choice (Strong, Moderate) • Combination of an echinocandin + LF-AmB may be considered based on animal studies and retrospective reports^{129,130} (Weak, Very Low) • AmB deoxycholate was historically the drug of choice but is associated with substantial nephrotoxicity and generally avoided in the current era^{80,132,133} (Strong, Moderate) <p>Maintenance therapy:</p> <ul style="list-style-type: none"> • Posaconazole or isavuconazonium^a sulfate (Weak, Moderate) 	<p>Induction therapy:</p> <ul style="list-style-type: none"> • Posaconazole or isavuconazonium sulfate^a for patients intolerant to or failing LF-AmB^{86,134,135} (Weak, moderate) • Combination of posaconazole + LF-AmB may be considered in refractory infections, but data are conflicting (Weak, Very Low) <p>Maintenance therapy:</p> <ul style="list-style-type: none"> • LF-AmB in patients who are clinically unstable or unable to tolerate oral intake

CMV Infection (Donor seropositive/Recipient seronegative)



Diagnostics are imperative; advanced diagnostics (sequencing) also very helpful

CMV is a common precursor to fungal infections

Voriconazole use may increase the risk of mucormycosis

Voriconazole-tacrolimus interaction drove tacrolimus levels up quite high/more immunosuppression

Fungal markers on blood not useful in this setting

Advanced susceptibility testing helps tailor therapy (Nocardia)

Mucormycosis is often a surgical emergency

Hickam's dictum often trumps Occam's razor

Numerous infections (viral, bacterial, fungal, Nocardia) all in one patient

Pneumonia on treatment for Aspergillus → two more pathogens, Rhizopus and Nocardia

Candida

Cryptococcus

Aspergillus

Agents of mucormycosis

Comments on “others”

Clinical syndrome

Diagnostics

Treatment

Prophylaxis

Prevention

Excellent surgical technique

Infection control

HEPA filters in hospital

Farming, gardening, other occupational/environmental exposures

Smoking marijuana

Prophylaxis

Primarily used for lung transplant: voriconazole, posaconazole, itraconazole

Also some heart, pancreas, and liver transplant: fluconazole, micafungin/caspofungin

Pretransplant: oral nystatin in liver patients on broad spectrum antibiotics (?)

Managing Fungal Sepsis Post-transplant

Conclusions

Low threshold to consider this potentially life threatening diagnosis
Careful consideration regarding prophylaxis and treatment
May be part of a cascade with other infections (i.e. CMV)
Guidelines from IDSA, AST ID COP, others can be very useful



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