

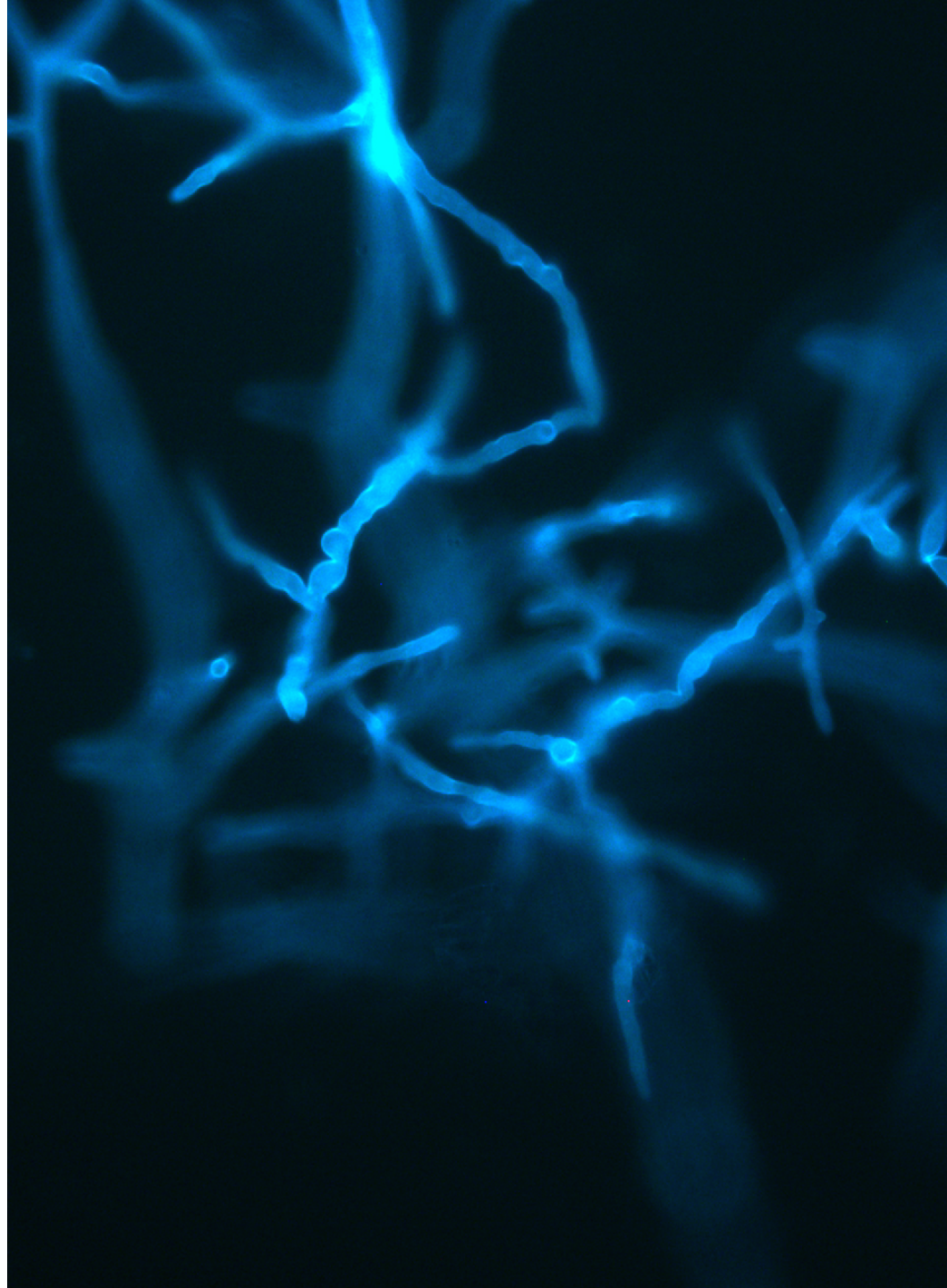
N.Klimko

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Immunology

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Medical University
Saint Petersburg, Russia

Contrasts between *mucormycosis* and *aspergillosis* in leukemia

8th Advances Against Aspergillosis
Lisboa Congress Centre, Lisbon, Portugal
3 February 2018



Disclosure

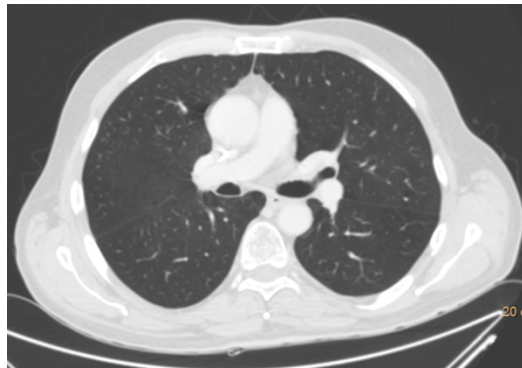


Anamnesis

- Male, 56 y
- Non-Hodgkin lymphoma
- 2015: x 6 DA-EPOCH-R + radiation therapy, 36 Gr
- 2017 – relapse
- April – June 2017 – x 3 ICE-R
- July – August 2017 – x 2 DHAP

September 2017, d +1-14

- BEAM + auto SCT ($2,8 \times 10^6$ /kg CD34+)
- D +2-14: voriconazole
- D + 4-13: severe neutropenia ($<0,5 \times 10^9$ /l)
- persisted lymphocytopenia ($<0,5 \times 10^9$ /l)
- D +4-13: neutropenic fever, meropenem +
- D +5: chest CT scan = N



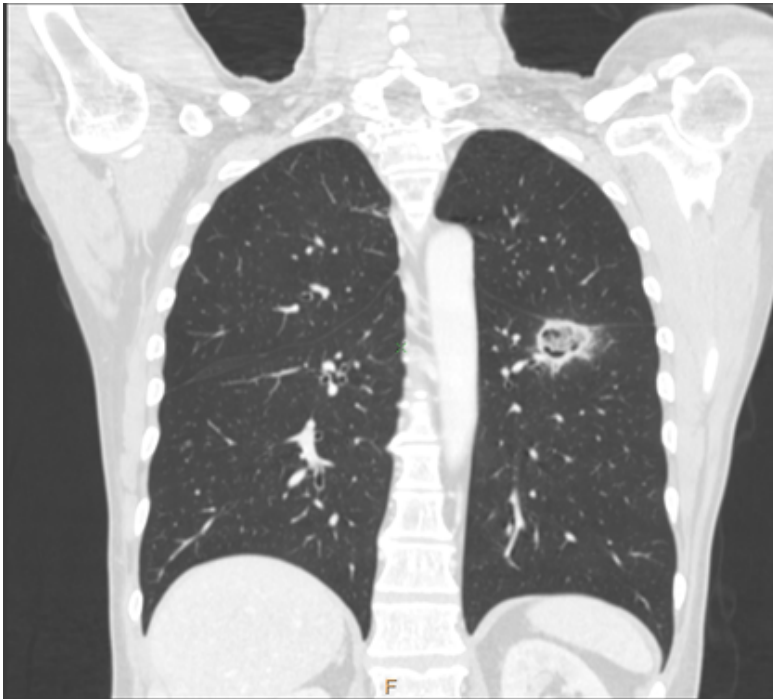
- D +6-7: intestinal bleeding, ICU, tygecycline +
- D +14: neutrophils $> 1,0 \times 10^9$ /l, $t = 37,0$ C⁰

October 2017, d +22

- satisfactory condition, $\uparrow t > 38^{\circ}$
- neu – $14,4 \times 10^9/l$, lymph $0,2 \times 10^9/l$, Hb 73 g/l, tr $19 \times 10^9/l$

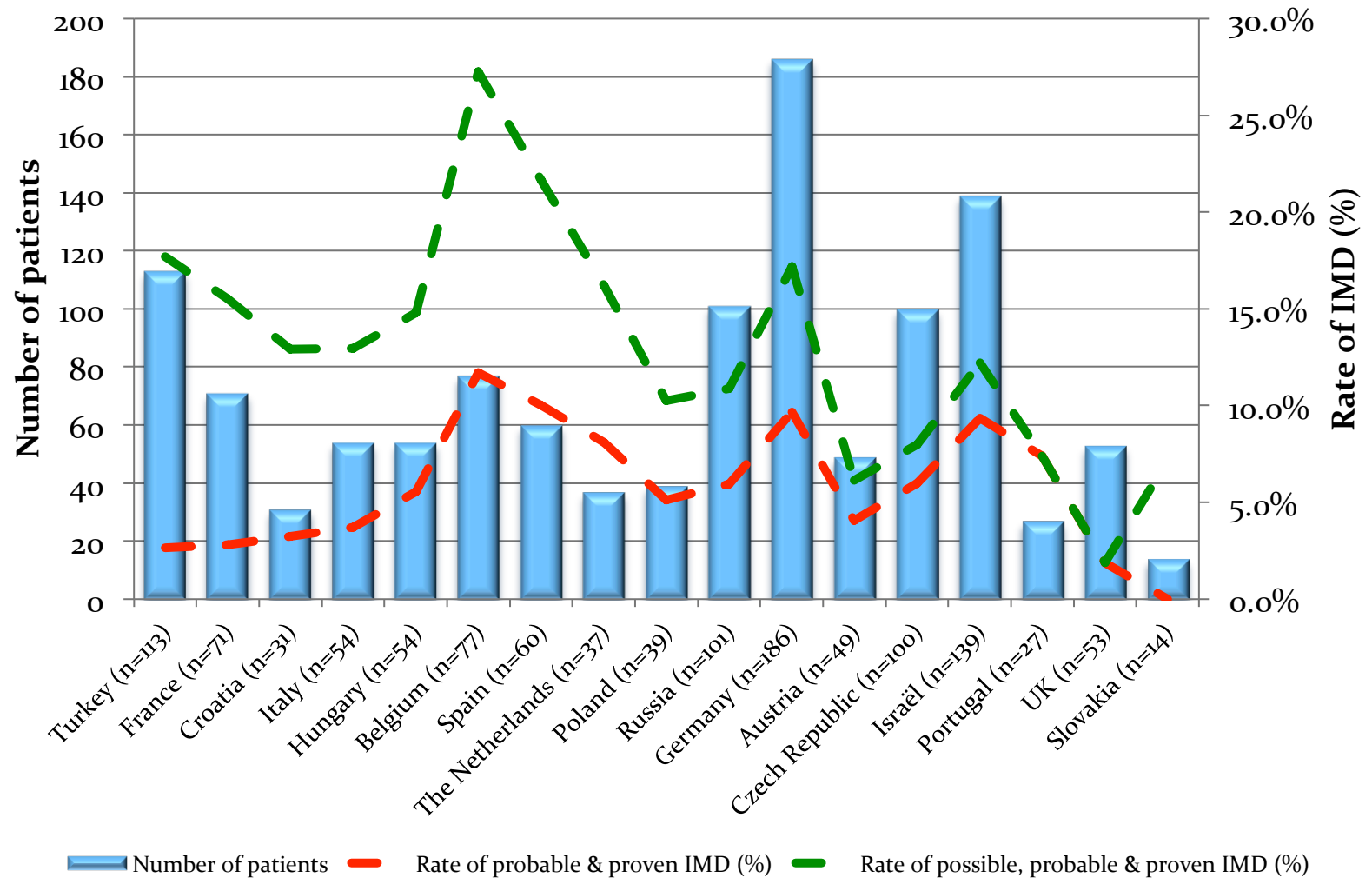
October 2017, d +22

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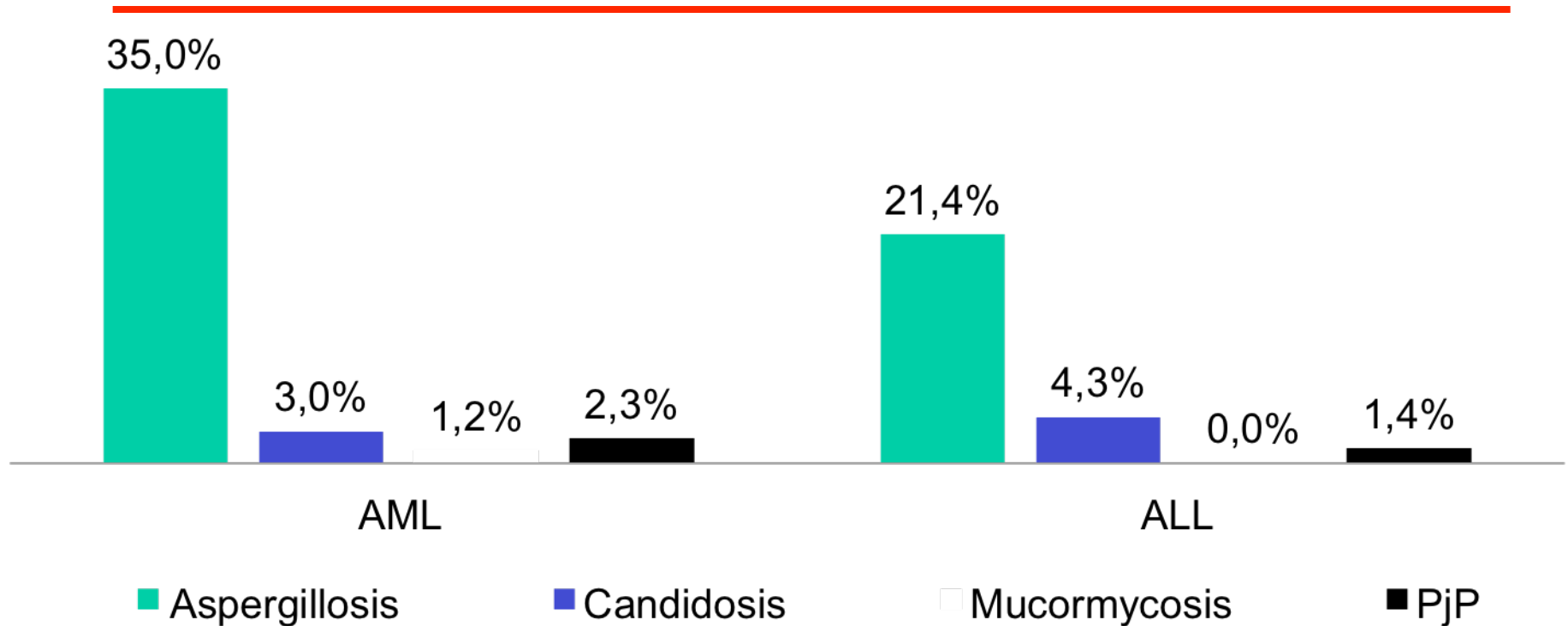


PIMDA

A European *P*rospective *I*nvasive *M*ould *D*isease Audit



Incidence of IFD in adult patients with AML/ALL 2003-14 yy, n=240



IA etiology

<i>Aspergillus fumigatus</i>	60%
<i>Aspergillus niger</i>	20%
<i>Aspergillus flavus</i>	20%

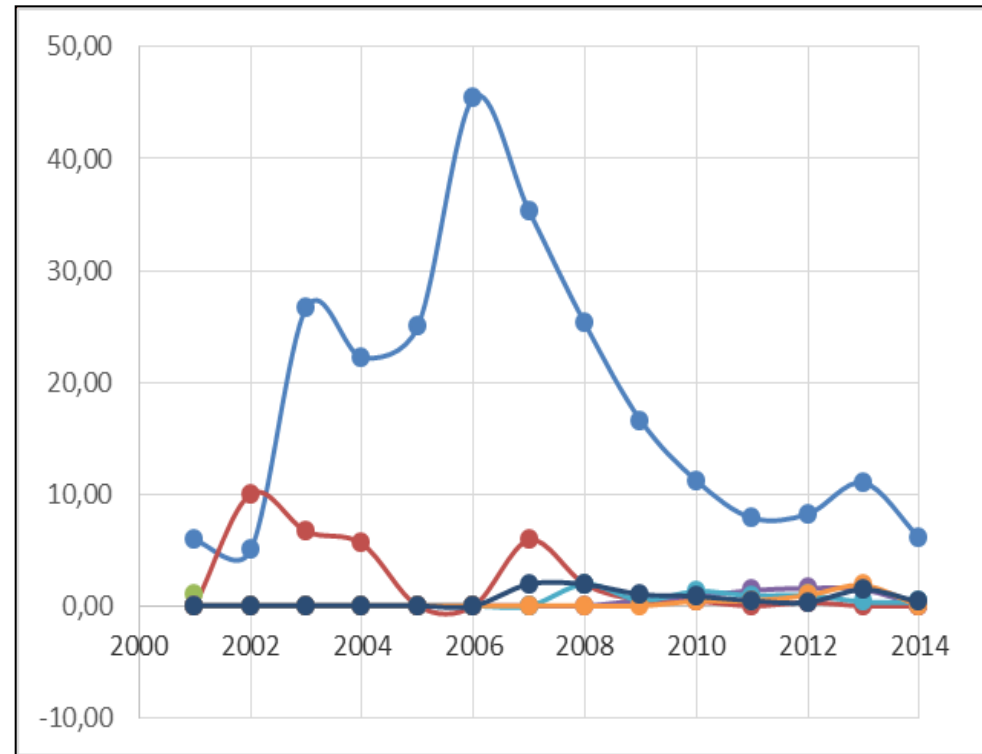
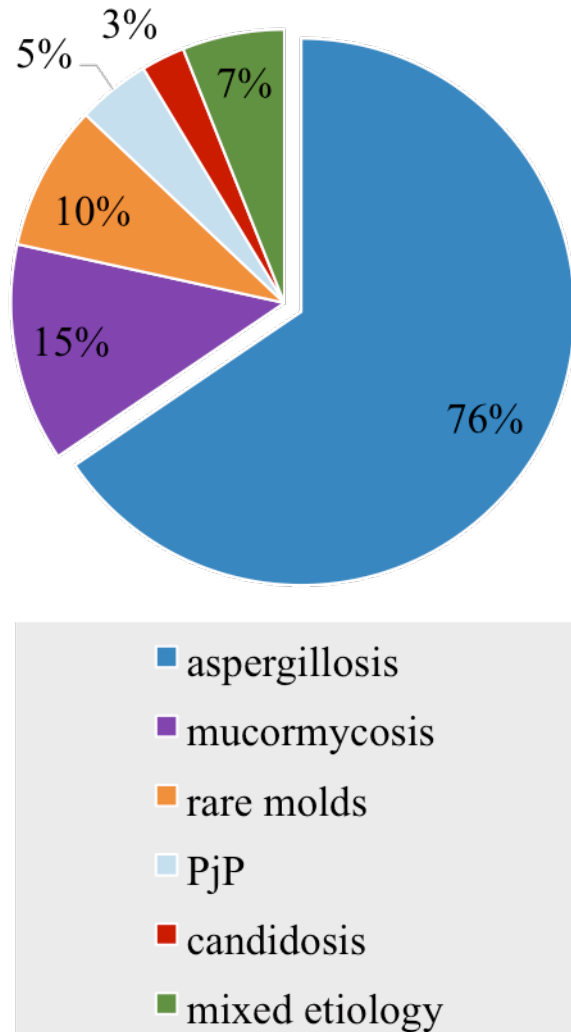
IC etiology

<i>Candida parapsilosis</i>	37%
<i>Candida guilliermondii</i>	25%
<i>Candida dubliniensis</i>	13%
<i>Candida norvegensis</i>	13%
<i>Candida krusei</i>	12%

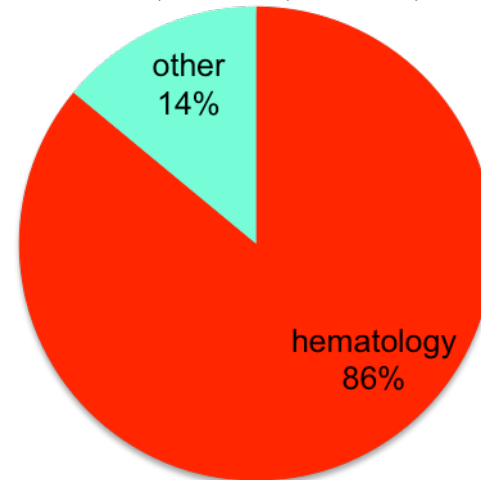
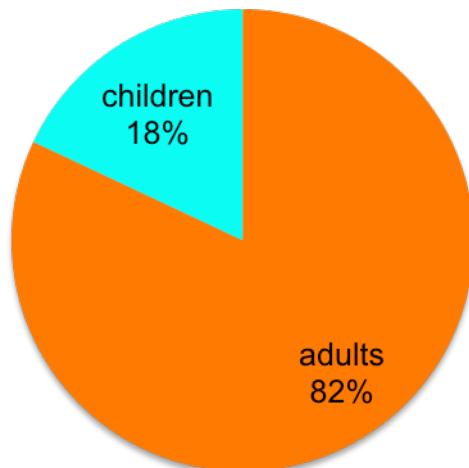
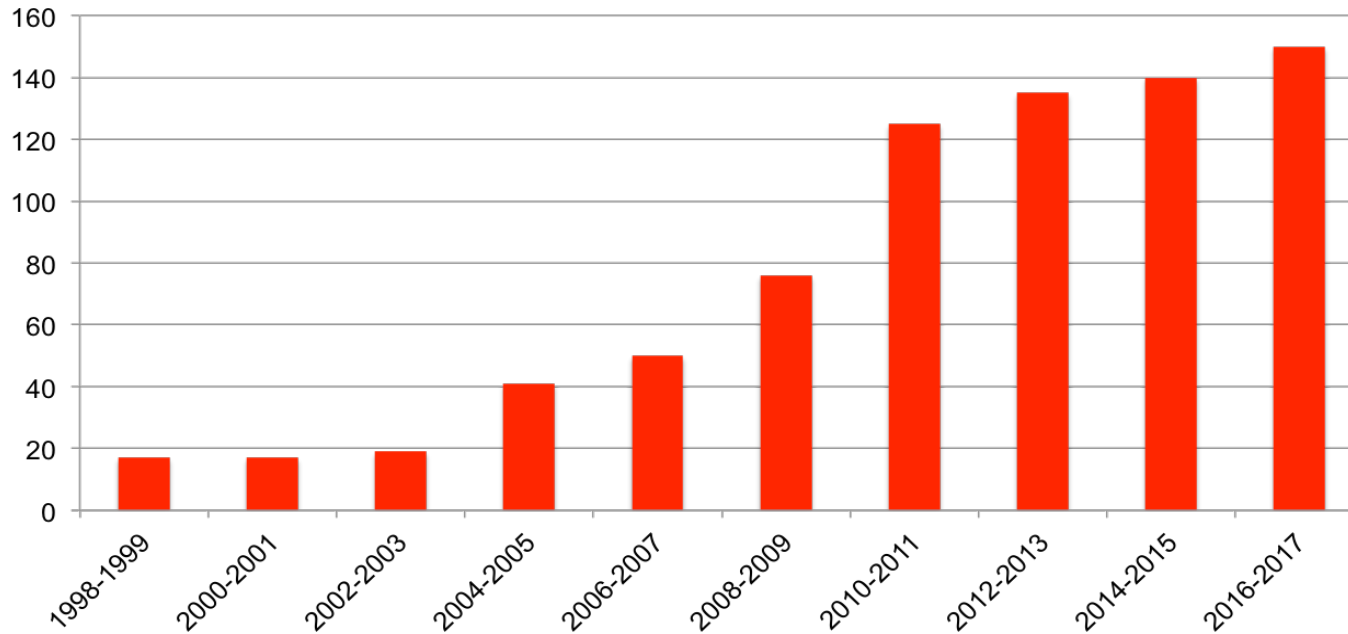
Mucormycosis etiology

<i>Rhizopus</i>	50%
<i>Lichtheimia corymbifera</i>	50%

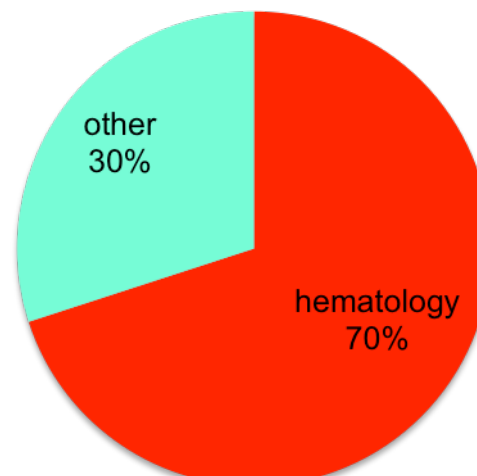
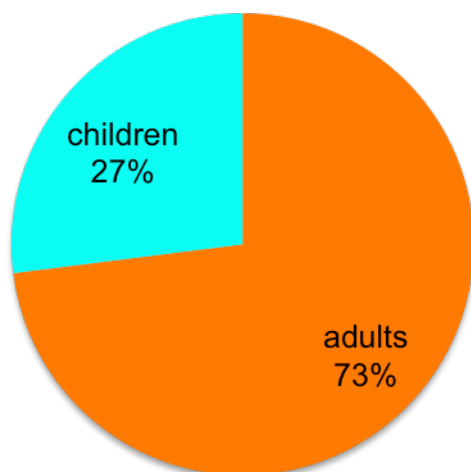
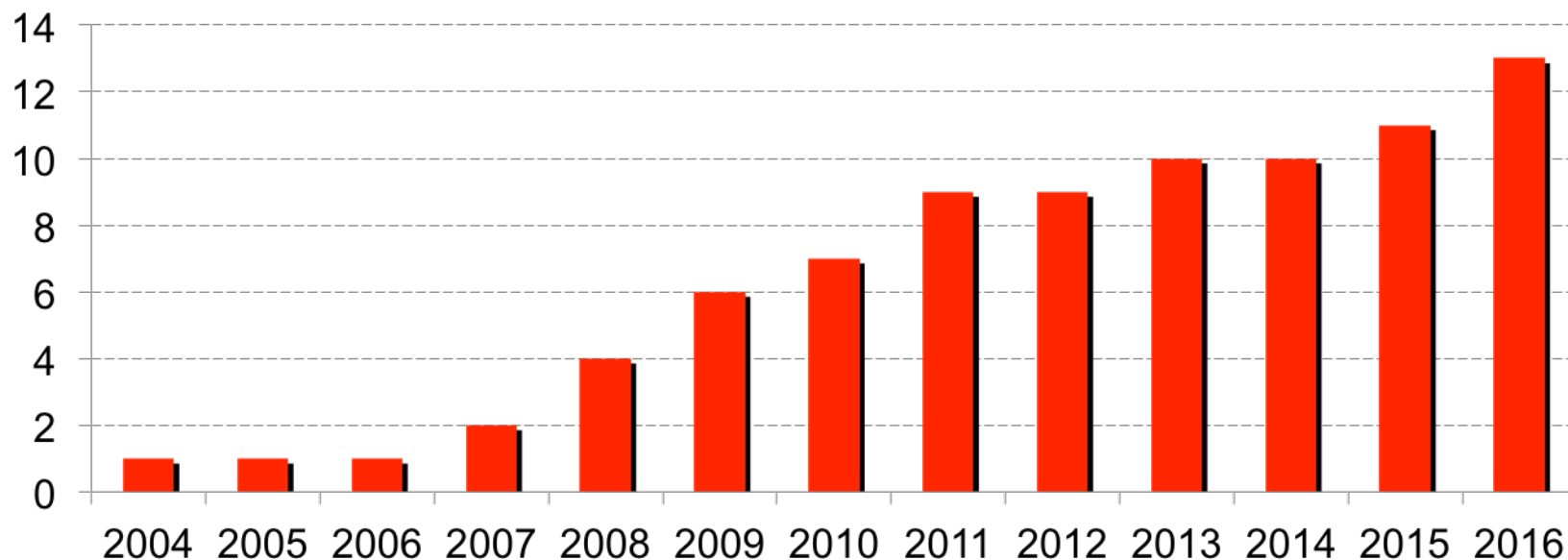
Incidence of IFD in pediatric patients after SCT 2000-2014, n=807



Invasive aspergillosis in Saint Petersburg, Russia registry, 1998 – 2017, n=700

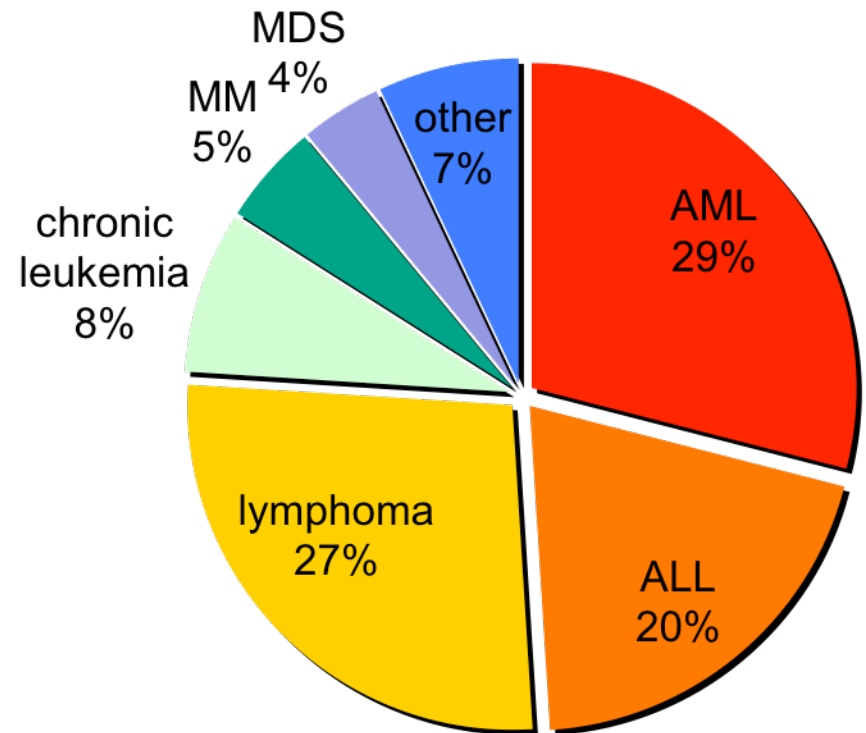
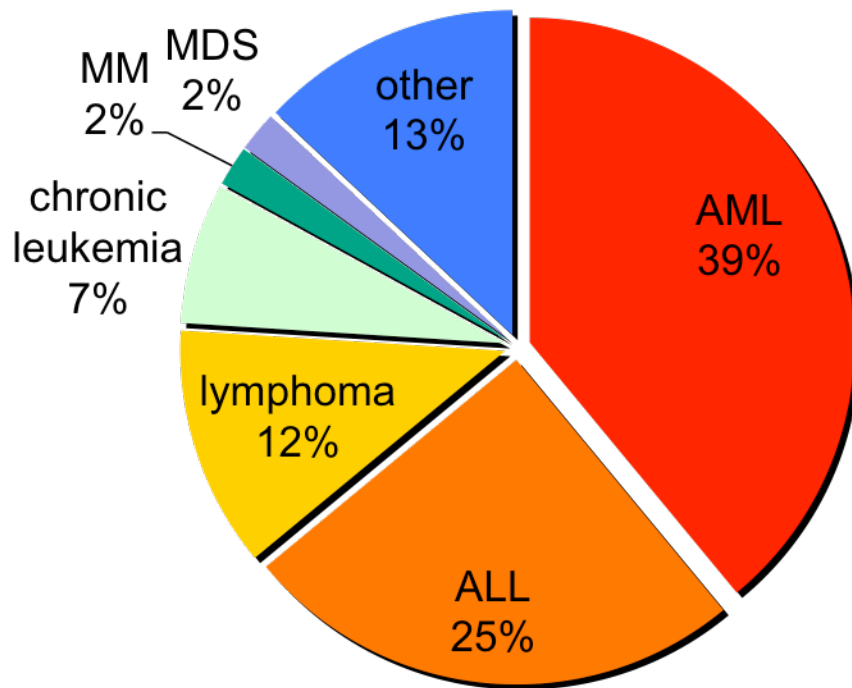


Mucormycosis in Saint Petersburg, Russia registry, 2004-2016, n=84



Mucormycosis vs Aspergillosis

hematology / underlying diseases

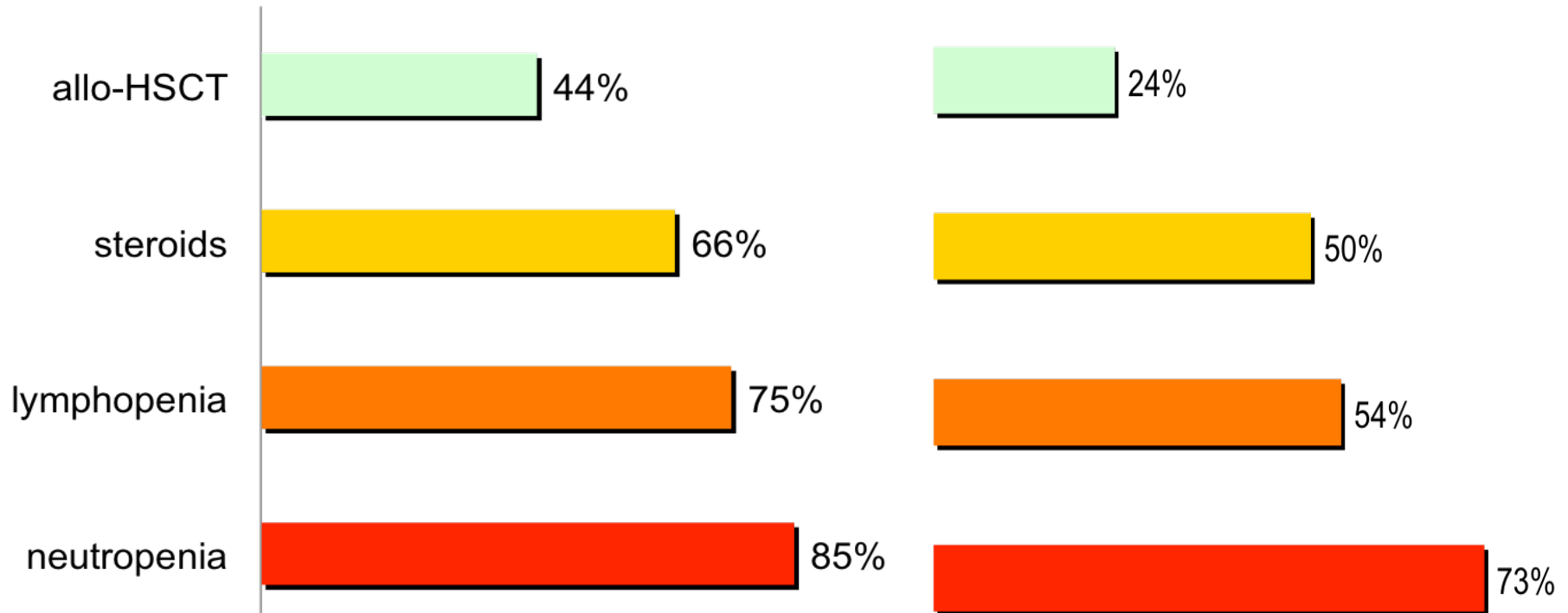


Klimko et al. Mucormycosis in oncohematology patients: results of the prospective study. Oncohematology, 2017

Shadrivova et al. Combination of invasive aspergillosis and mucormycosis in hematological patients. P 65, AAA8, 2018

Mucormycosis vs Aspergillosis

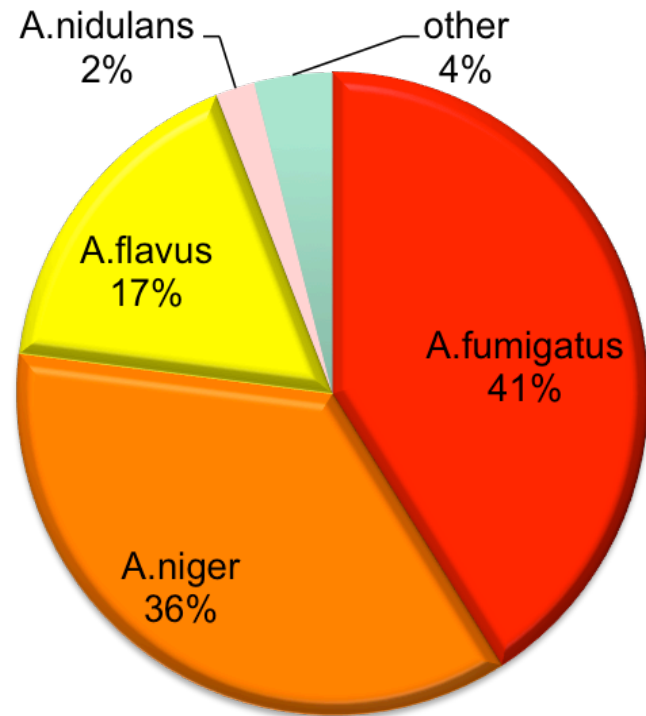
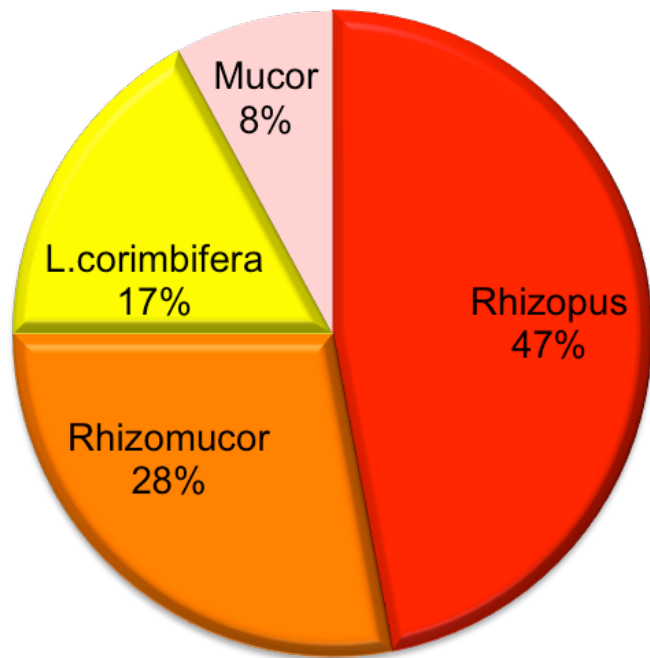
hematology / risk factors



- median of severe neutropenia – 30 vs 15 days
- median of lymphocytopenia – 30 vs 15 days
- mucormycosis was diagnosed in 1–225 days after IA - 52% patients

Mucormycosis vs Aspergillosis

hematology / etiology



Mucormycosis vs Aspergillosis

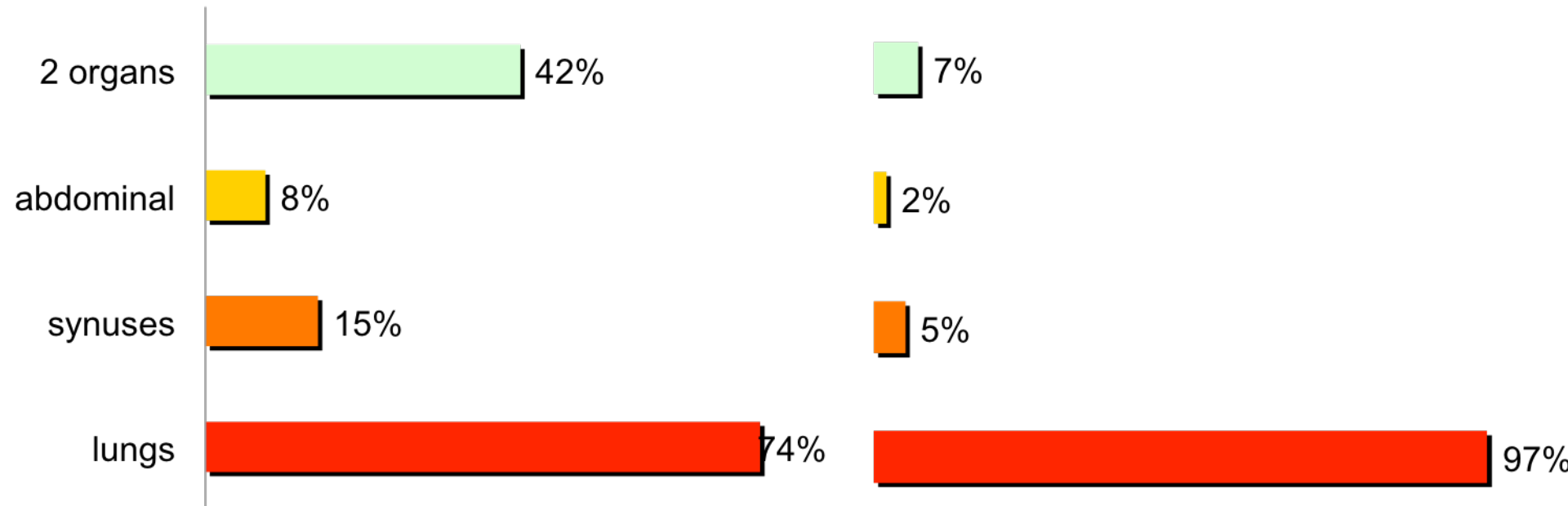
in vitro susceptibility of pathogenic fungi

Table 3 Susceptibility of pathogenic fungi without acquired resistance mechanisms

	<i>Amphotericin</i>	<i>Echinocandins</i>	<i>Fluconazole</i>	<i>Itraconazole</i>	<i>Voriconazole</i>	<i>Posaconazole</i>	5-FC
<i>Candida</i>							
<i>C. albicans</i>	S	S	S	S	S	S	S
<i>C. glabrata</i>	S	S	I-R ^a	S-I-R ^a	S-I-R ^a	S-I-R ^a	S
<i>C. krusei</i>	S	S	R	I-R	S-I-R ^a	S-I-R ^a	R
<i>C. parapsilosis</i>	S	S-I	S	S	S	S	S
<i>C. tropicalis</i>	S	S	S	S	S	S	S
<i>Cryptococcus</i>	S	R	S ^b	S	S	S	S
<i>Trichosporon</i>	S-I-R	R	I-R	I-R	S	S	R
<i>Aspergillus</i>							
<i>A. fumigatus</i>	S	S	R	S	S	S	R
<i>A. terreus</i>	I-R	S	R	S	S	S	R
<i>Fusarium</i>	S	R	R	R	S-I-R	S-I-R	R
<i>S. apiospermum</i> ^c	R	R	R	R	S-I	S-I	R
<i>S. prolificans</i> ^c	R	R	R	R	I-R	I-R	R
<i>Zygomycetes</i>	S-I-R	R	R	R	R	S-I-R	R

Mucormycosis vs Aspergillosis

hematology / sites of infection

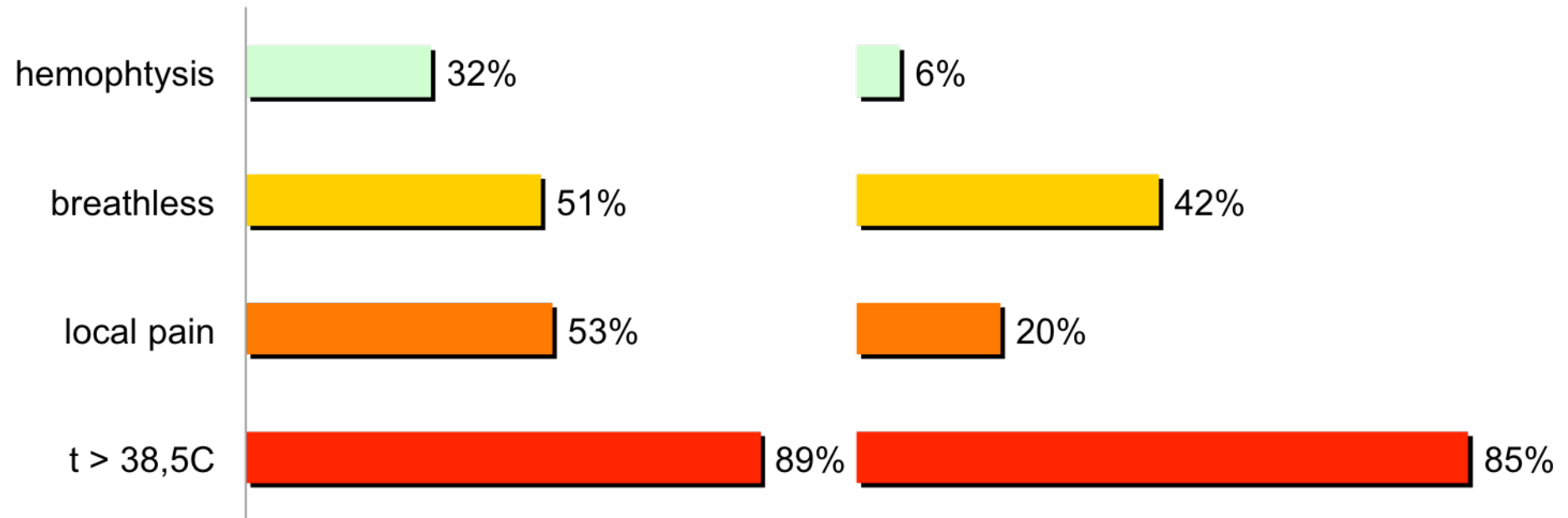


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Shadrivova et al. Combination of invasive aspergillosis and mucormycosis in hematological patients. P 65, AAA8, 2018

Mucormycosis vs Aspergillosis

hematology / symptoms



Mucormycosis in Saint Petersburg, Russia

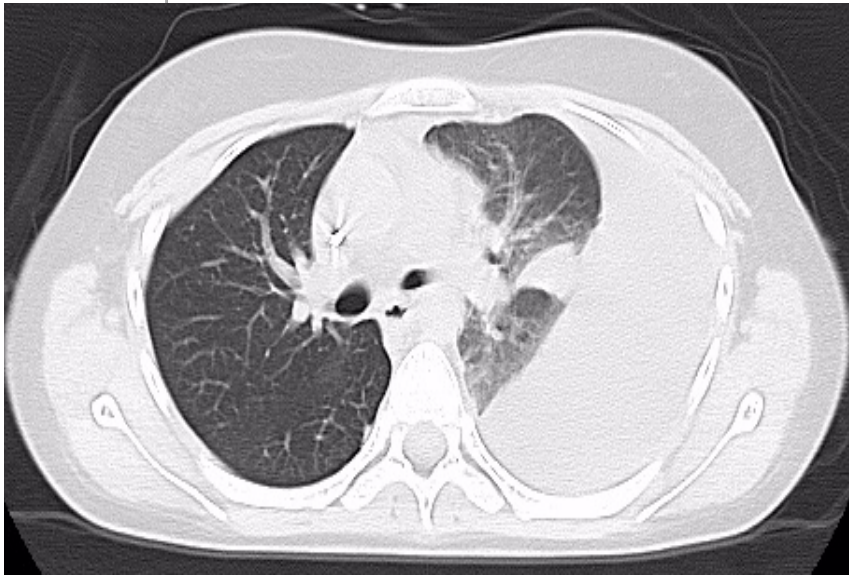
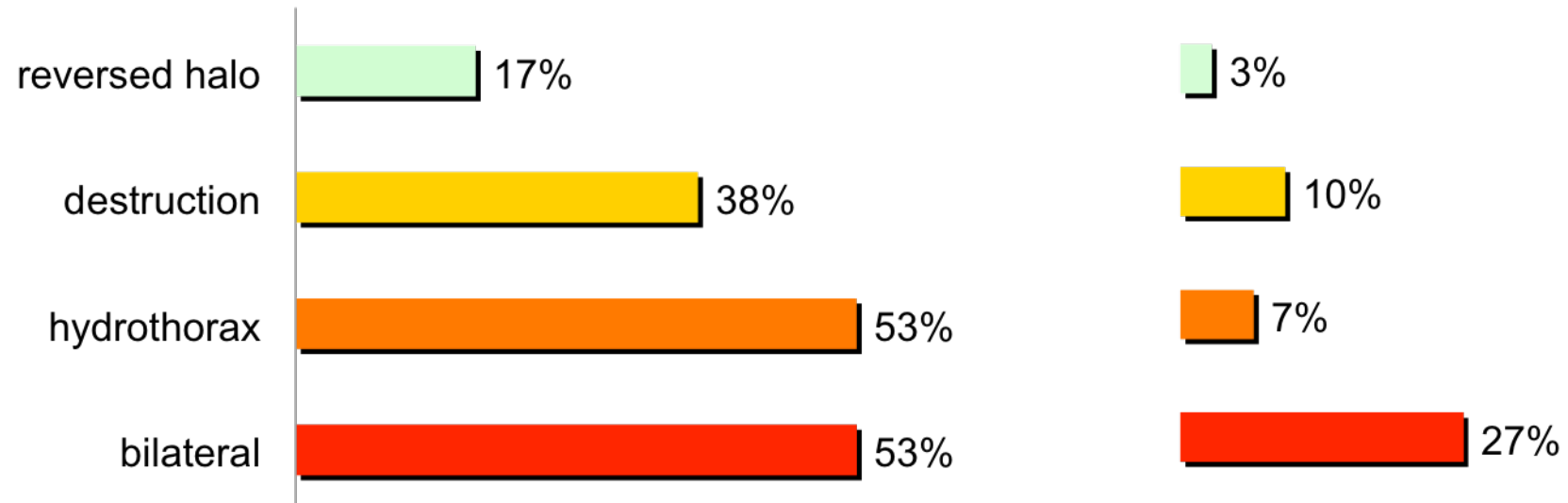


Mucormycosis in Saint Petersburg, Russia



Mucormycosis vs Aspergillosis

hematology / CT scan

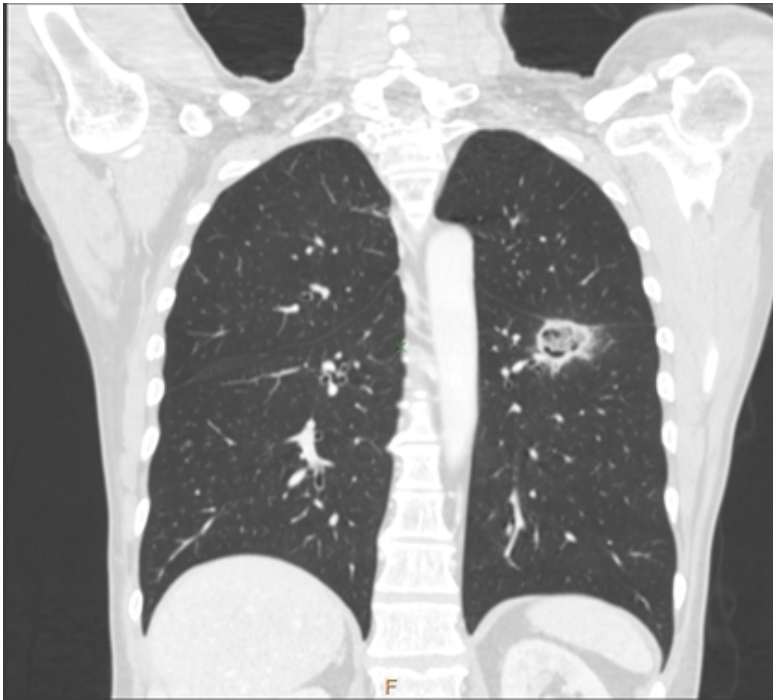


Klimko et al. Mucormycosis in oncohematology patients: results of the prospective study. *Oncohematology*, 2017

Shadrivova et al. Combination of invasive aspergillosis and mucormycosis in hematological patients. *P 65, AAA8*, 2018

October 2017, d +22

- satisfactory condition, $\uparrow t > 38^{\circ}$
- neu – $14,4 \times 10^9/l$, lymph $0,2 \times 10^9/l$, Hb 73 g/l, tr $19 \times 10^9/l$



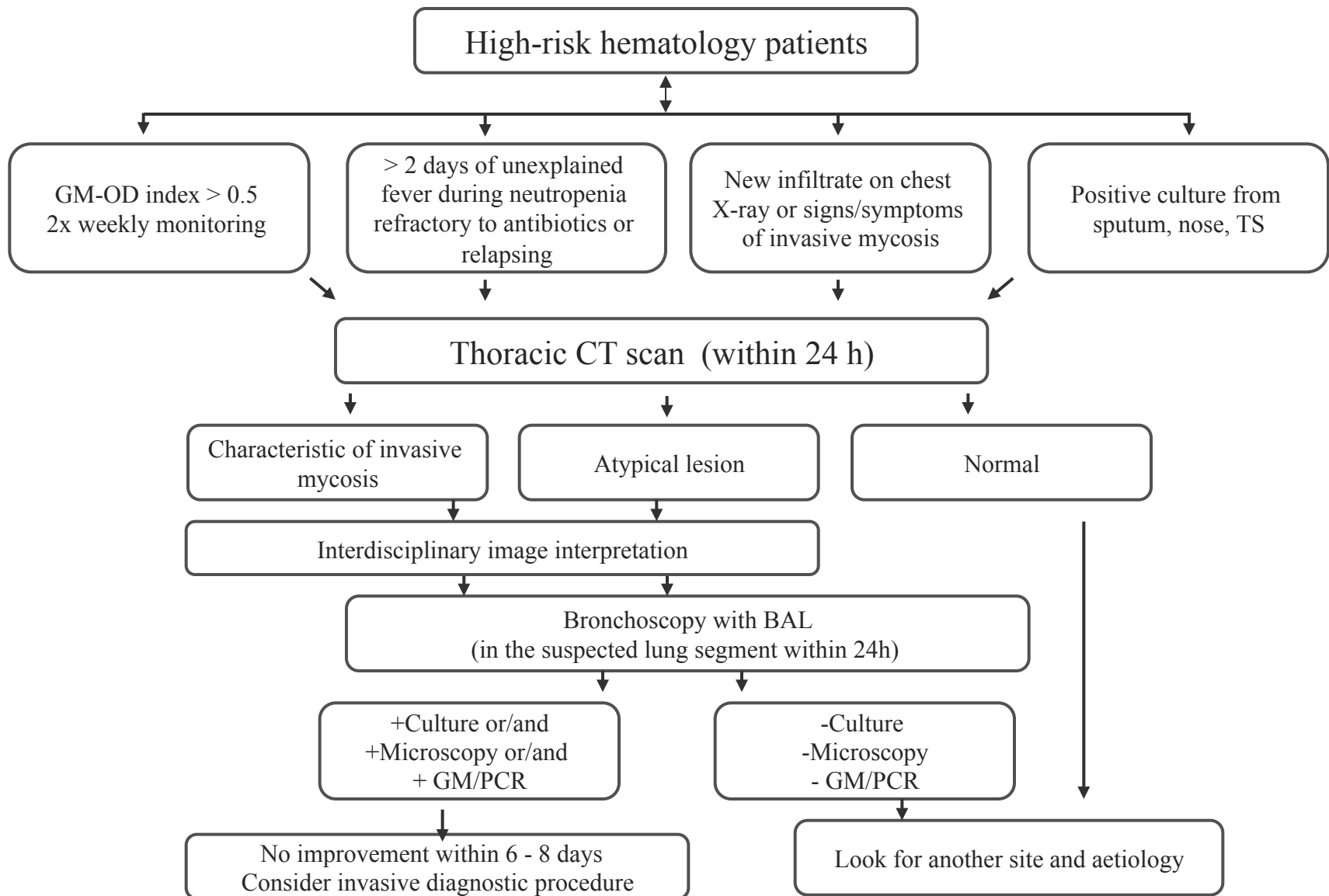
Invasive aspergillosis diagnostic algorithm



EFISG

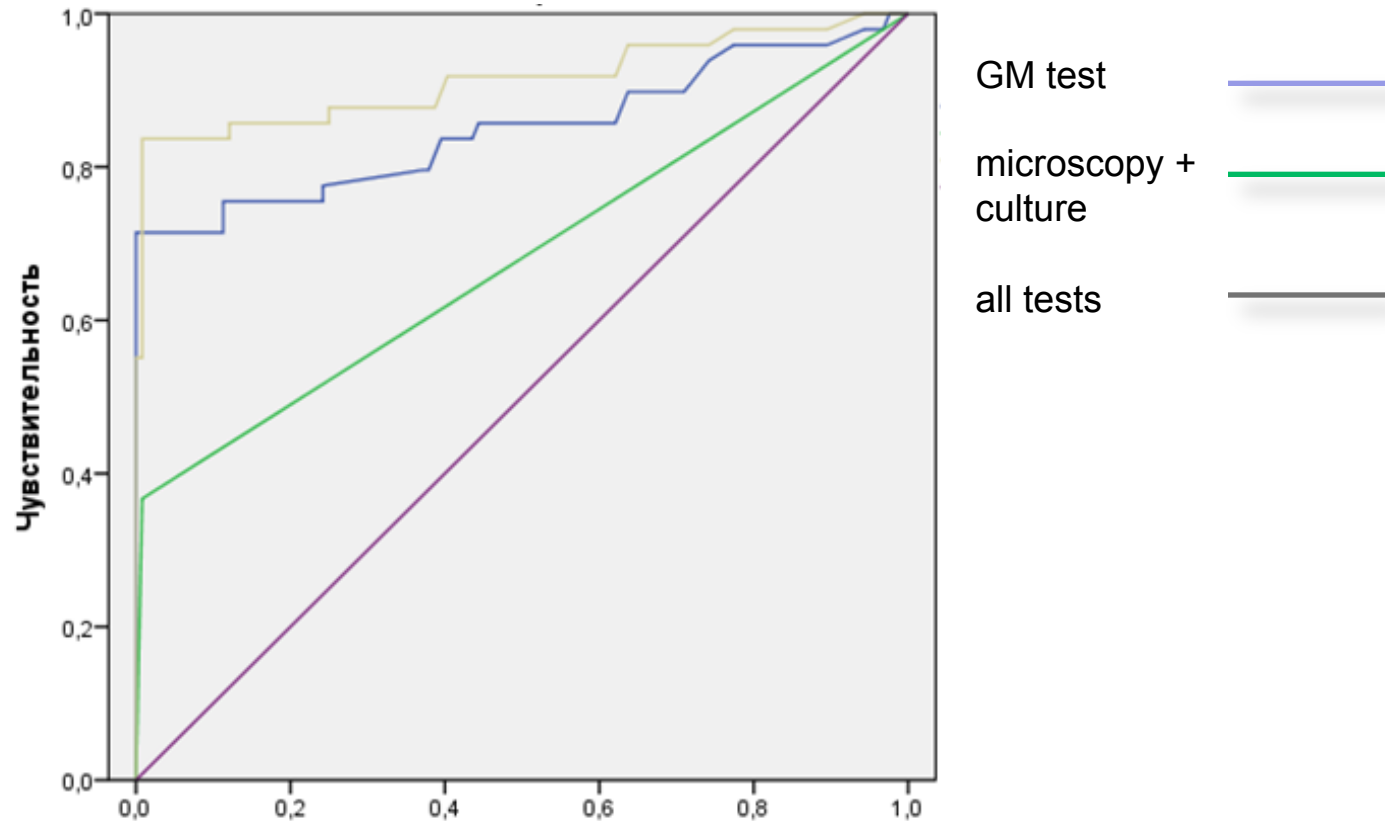
European Society of Clinical Microbiology and Infectious Diseases

ESCMID FUNGAL INFECTION
STUDY GROUP



Invasive aspergillosis in Saint Petersburg, Russia

BAL: GM test, microscopy and culture

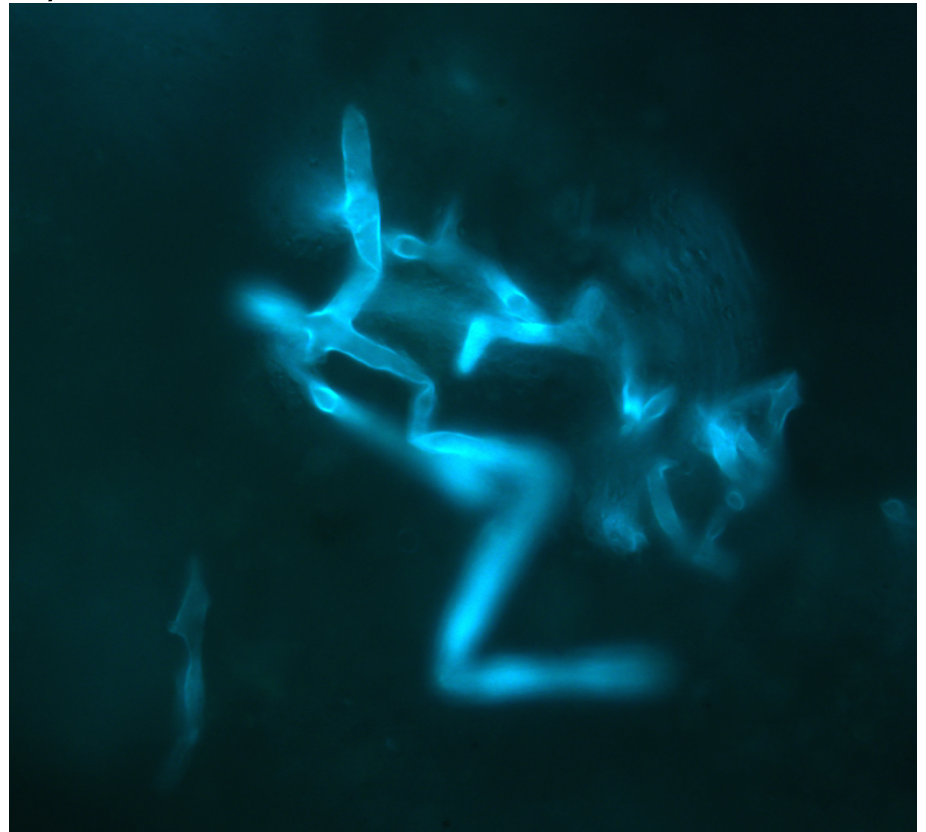


October 2017, d +23

- GM test serum – negative (0,11)
- Bronchoscopy (tr=17x10⁹/l)
- GM test BAL – negative (0,16)
- Culture BAL – negative

October 2017, d +23

- GM test serum – negative (0,11)
- Bronchoscopy (tr=17x10⁹/l)
- GM test BAL – negative (0,16)
- Culture BAL – negative
- Microscopy BAL – positive



ECIL-6 recommendations for first-line treatment of invasive aspergillosis

Table 7. ECIL-6 recommendations for first-line treatment of invasive aspergillosis.

	Grade	Comments
Voriconazole ^a	A I	Daily dose: 2x6 mg/kg on day 1 then 2x4 mg/kg (initiation with oral therapy: C III)
Isavuconazole	A I	As effective as voriconazole and better tolerated
Liposomal amphotericin B	B I	Daily dose: 3 mg/kg
Amphotericin B lipid complex	B II	Daily dose: 5 mg/kg
Amphotericin B colloidal dispersion	C I	Not more effective than d-AmB but less nephrotoxic
Caspofungin	C II	
Itraconazole	C III	
Combination voriconazole ^a + anidulafungin	C I	
Other combinations	C III	
Recommendation against use		
Amphotericin B deoxycholate	A I	Less effective and more toxic

^aMonitoring of serum levels is indicated. In the absence of sufficient data for first-line monotherapy, anidulafungin, micafungin and posaconazole have not been graded.

ECIL-6 recommendations for first line therapy of mucormycosis

Table 9. ECIL-6 recommendations for first-line therapy of mucormycosis.

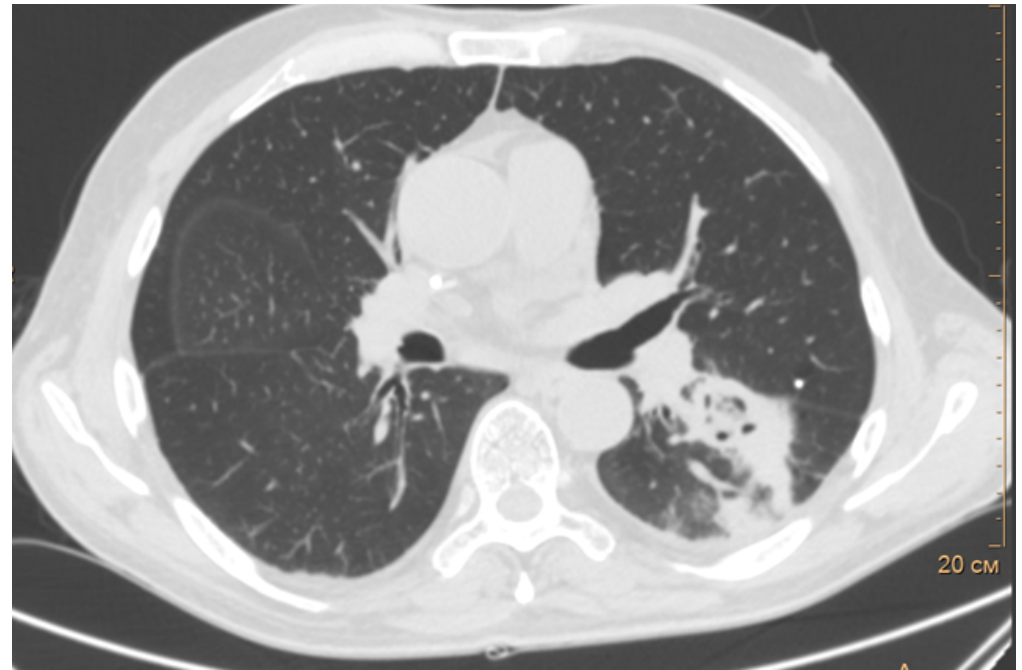
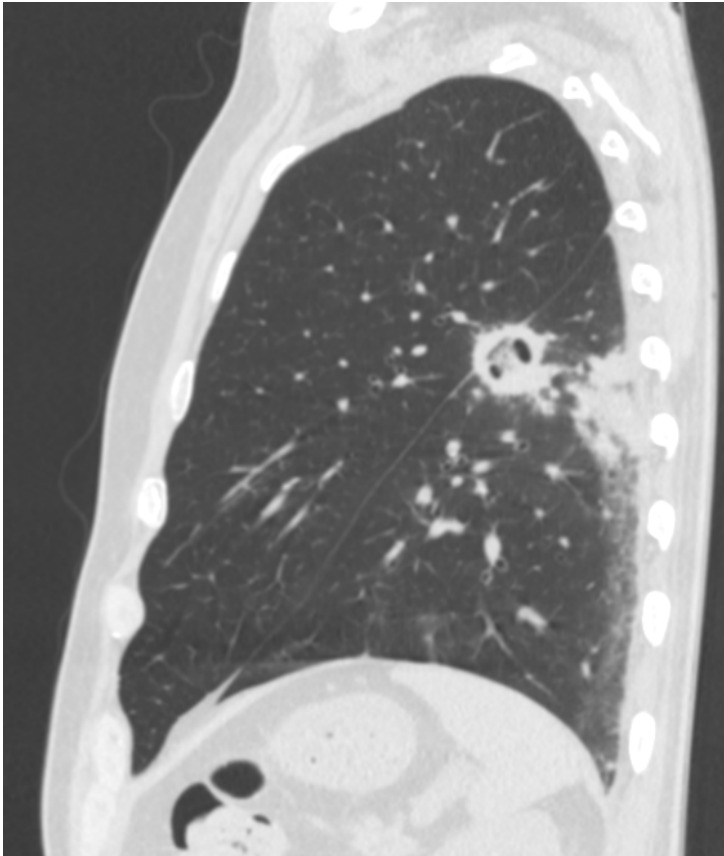
	Grade	Comments
Management includes antifungal therapy, surgery and control of underlying conditions	A II	Multidisciplinary approach is required
Antifungal therapy		
Amphotericin B deoxycholate	C II	Daily dose: 5 mg/kg. Liposomal amphotericin B should be preferred in CNS infection and/or renal failure
Liposomal amphotericin B	B II	
Amphotericin B lipid complex	B II	No data to support its use as first-line treatment. Alternative when amphotericin B formulations are absolutely contraindicated.
Amphotericin B colloidal dispersion	C II	
Posaconazole	C III	
Combination therapy	C III	
Control of underlying condition	A II	Includes control of diabetes, hematopoietic growth factor if neutropenia, discontinuation/tapering of steroids, reduction of immunosuppressive therapy
Surgery		
Rhino-orbito-cerebral infection	A II	Surgery should be considered on a case by case basis, using a multi-disciplinary approach
Soft tissue infection	A II	
Localized pulmonary lesion	B III	
Disseminated infection	C III	
Hyperbaric oxygen	C III	
Recommendation against use		
Combination with deferasirox	A II	

CNS: central nervous system.

October 2017, d +23

- $t = 38,5^{\circ} \text{C}$
- neu $9,5 \times 10^9/\text{l}$, lymph $0,3 \times 10^9/\text{l}$, Hb 72 g/l, tr $17 \times 10^9/\text{l}$
- lipid AmB 3 mg/kg/d + caspofungin 70 → 50 mg/d

October 2017, d +27



ECIL-6 recommendations for salvage and maintenance therapy of mucormycosis

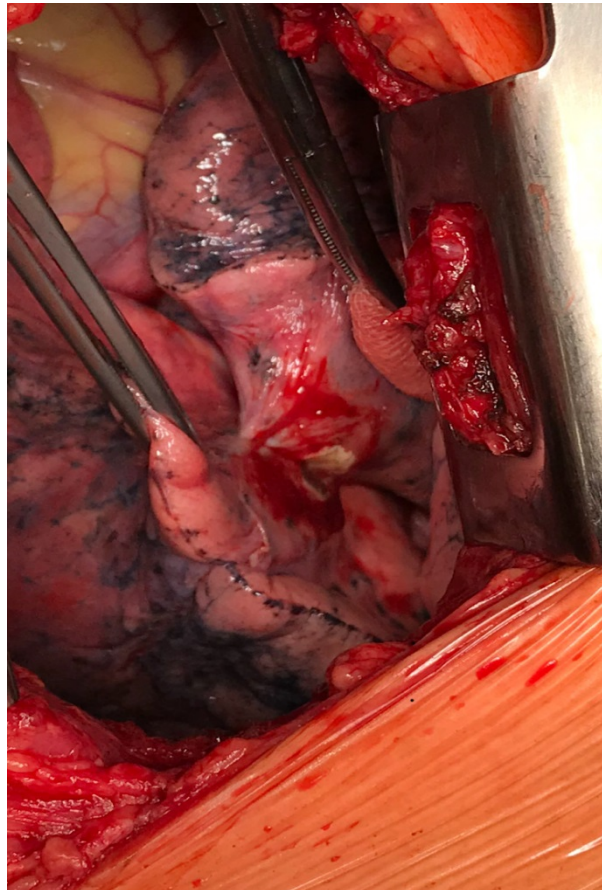
Table 10. ECIL-6 recommendations for salvage and maintenance therapy of mucormycosis.

	Grade	Comments
Salvage therapy		
Management includes antifungal therapy, control of underlying disease and surgery	A II	
Posaconazole	B II	
Combination of lipid amphotericin B and caspofungin	B III	
Combination of lipid amphotericin B and posaconazole	B III	
Maintenance therapy		
Posaconazole	B III	Overlap of a few days with first-line therapy to obtain appropriate serum levels. Monitoring of serum levels might be indicated ^a

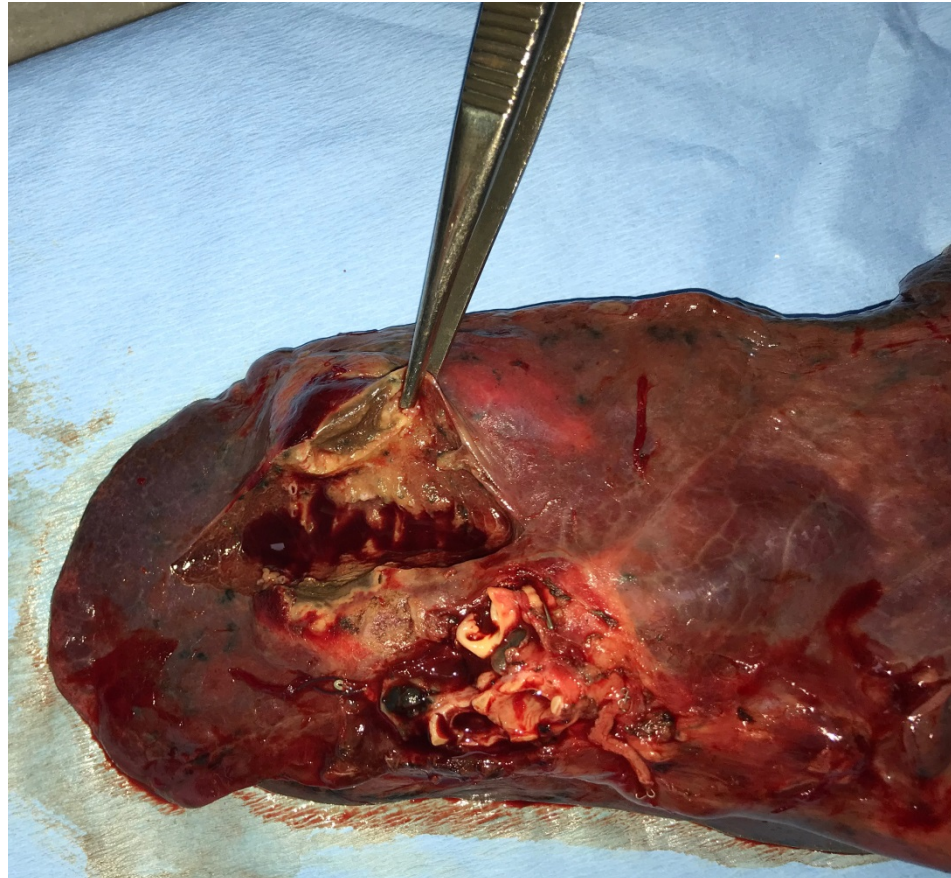
^aBoth comments apply to the oral solution but may not apply to the solid oral formulation.

October 2017, d +28

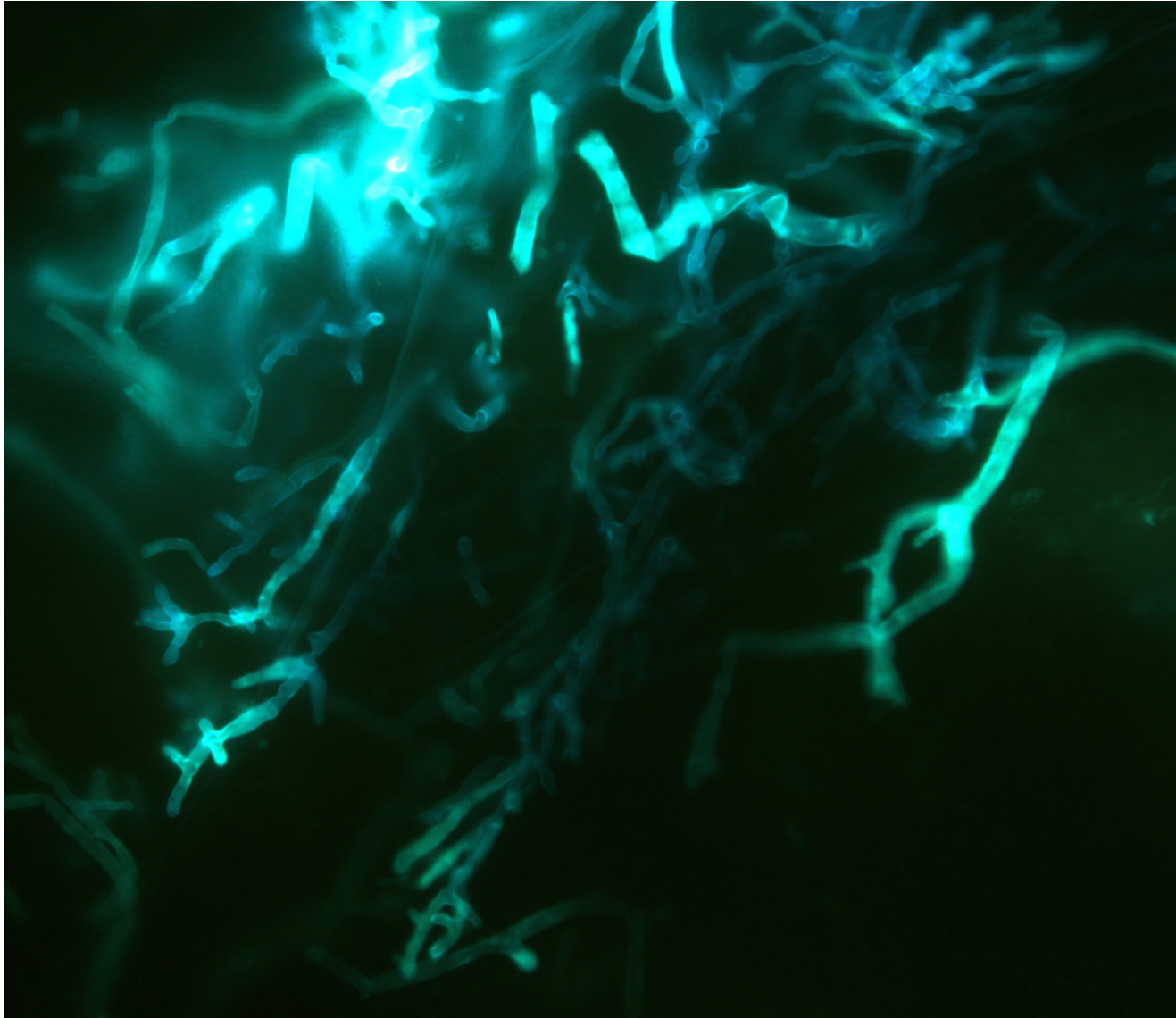
- Tr=22x10⁹/l
- lower lobectomy with marginal resection of the upper lobe of the left lung



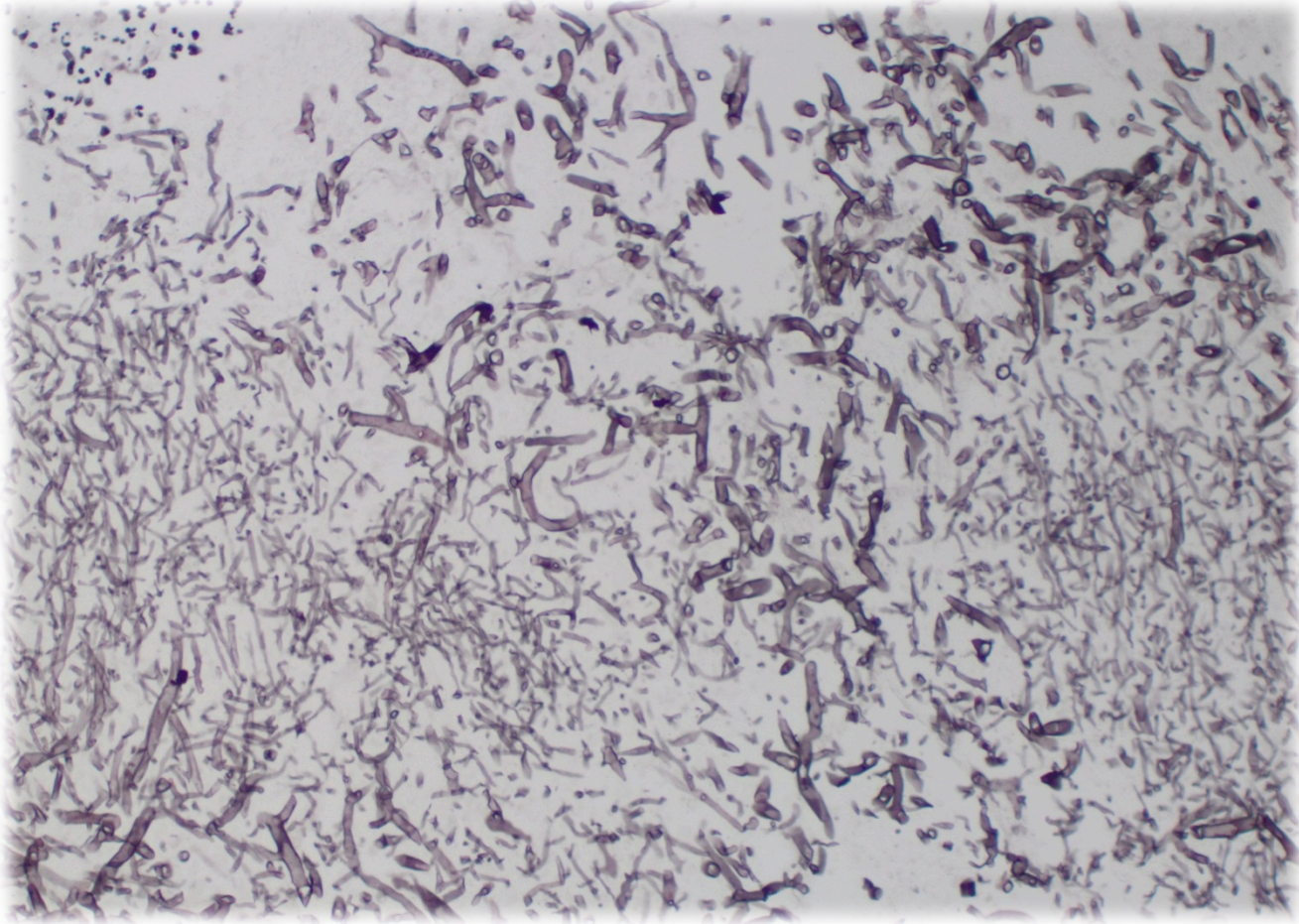
October 2017, d +28



October 2017, d +28



October 2017, d +28



October 2017, d +28



- *Lichtheimia corymbifera*

October 2017 – February 2018

- D +28-33: lipid AmB 3 mg/kg/d + caspofungin 70 50 mg/d + posaconazole 800 mg/d
- D +34: neu $2,1 \times 10^9/\text{l}$, lymph $1,3 \times 10^9/\text{l}$, Hb 73 g/l, tr $41 \times 10^9/\text{l}$
- D +34: CT scan



- D +34: posaconazole 800 mg/d – 3 months
- February 2018 – good condition, remission of NHL

Question

/s mucormycosis or aspergillosis a contraindication for allo-SCT?

- yes
- no

Question

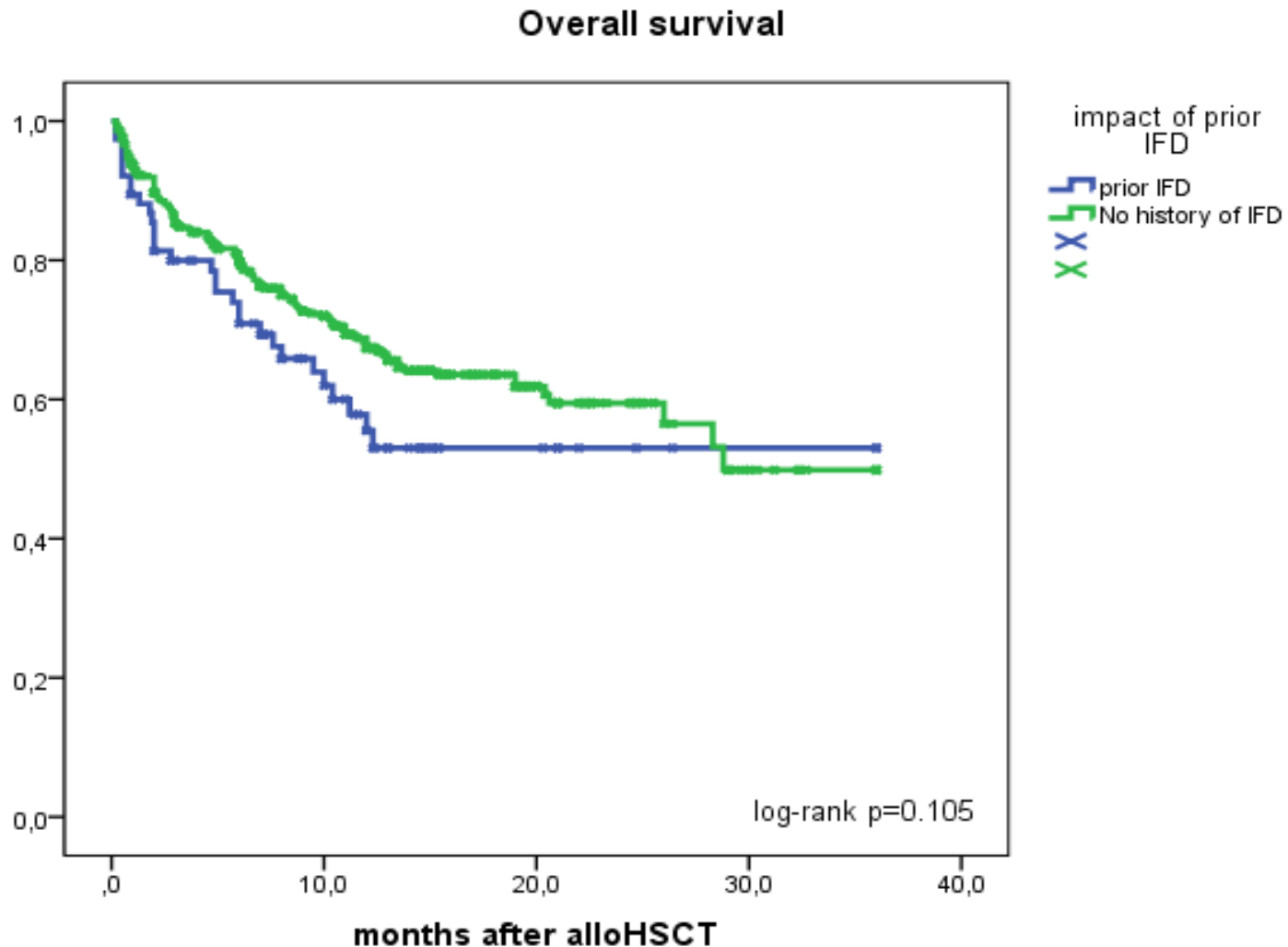
/s mucormycosis or aspergillosis a contraindication for allo-SCT?

- yes

- no

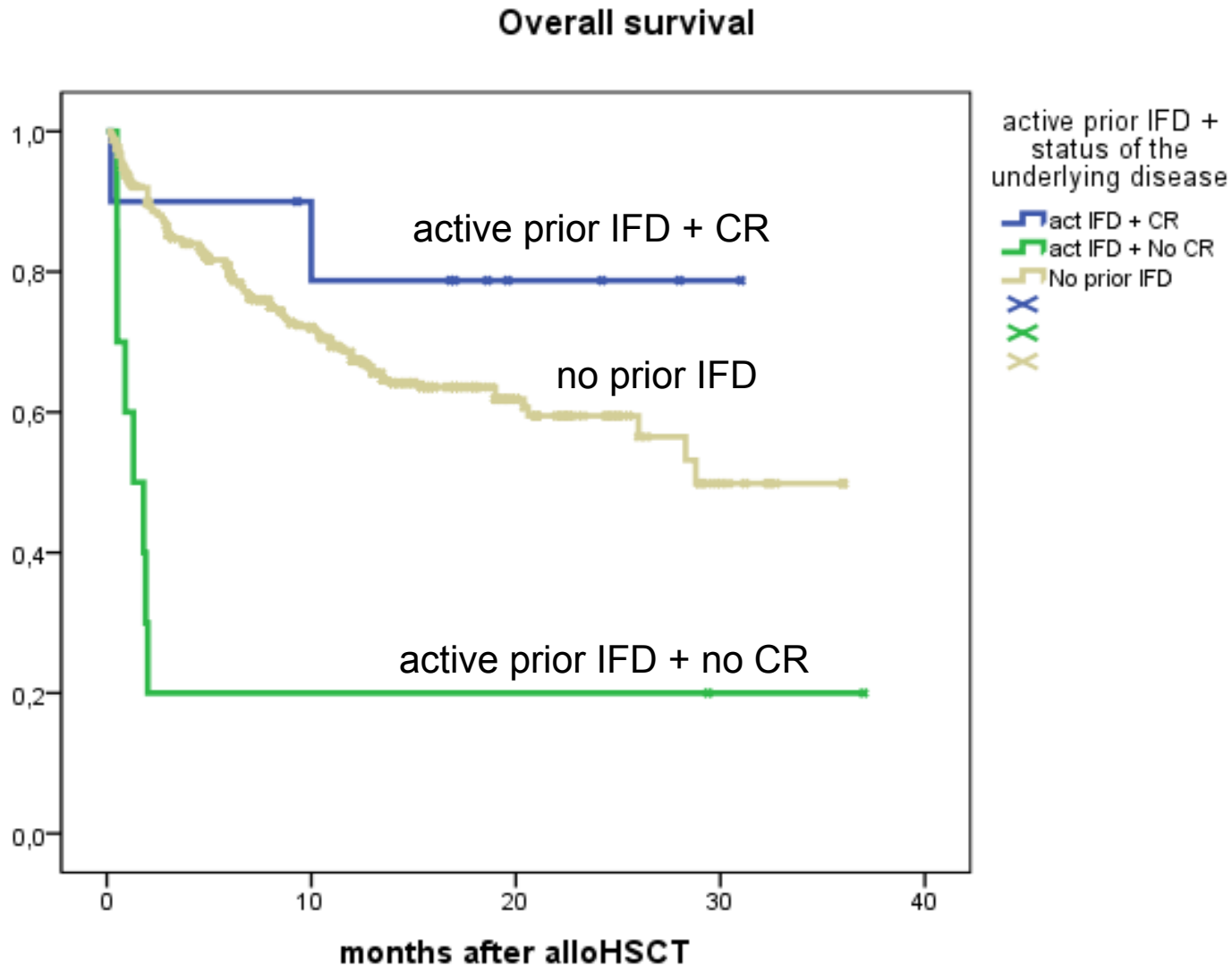
Allo-SCT in patients with prior IFD

overall survival rate (2013-16, n=504)



Allo-SCT in patients with prior IFD

overall survival rate (2013-16, n=504)





8th ADVANCES AGAINST ASPERGILLOSIS

Lisbon, Portugal

1 - 3 February 2018

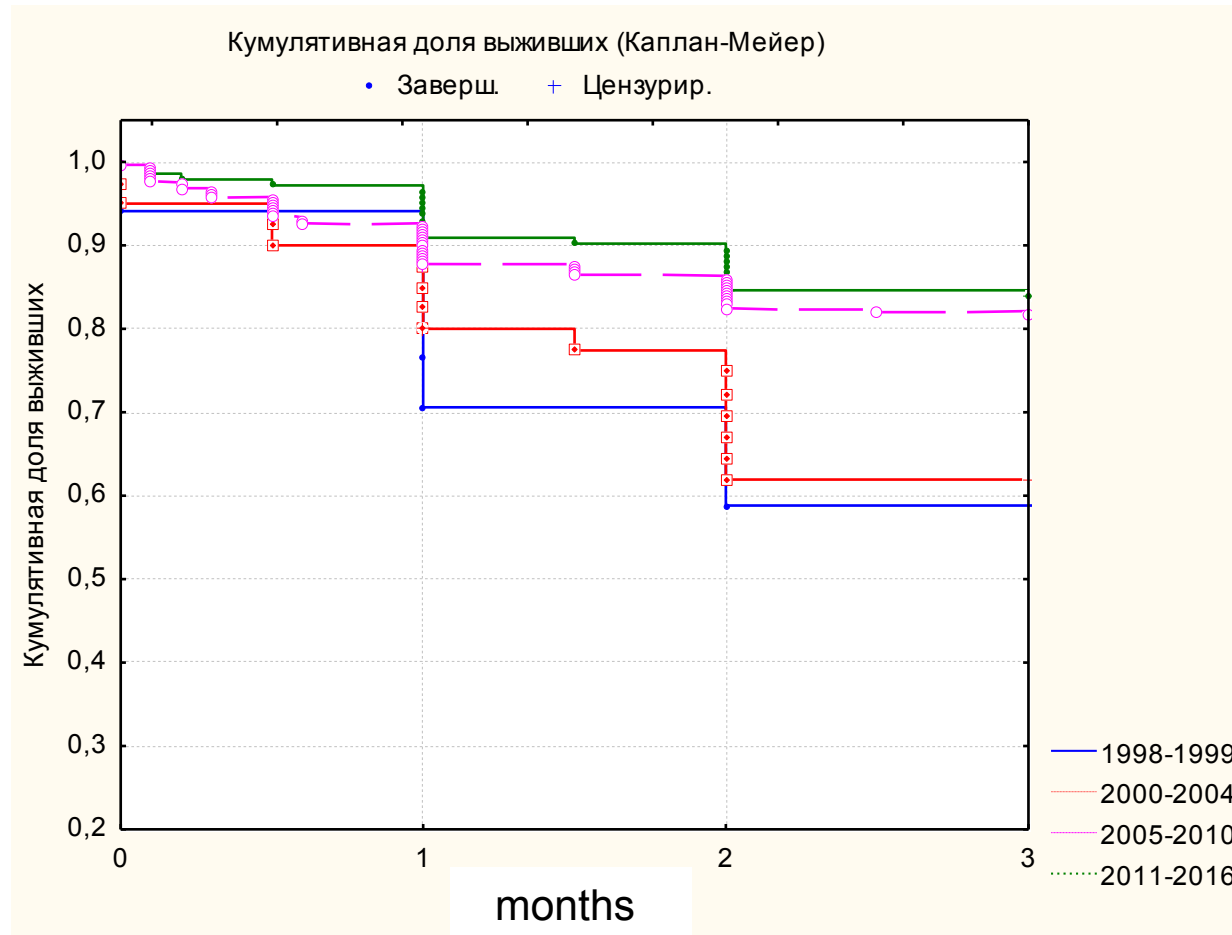
Lisbon Congress Centre



Aspergillosis Target 1:

**Survival in invasive aspergillosis increased to 90%
(up from under 50%)**

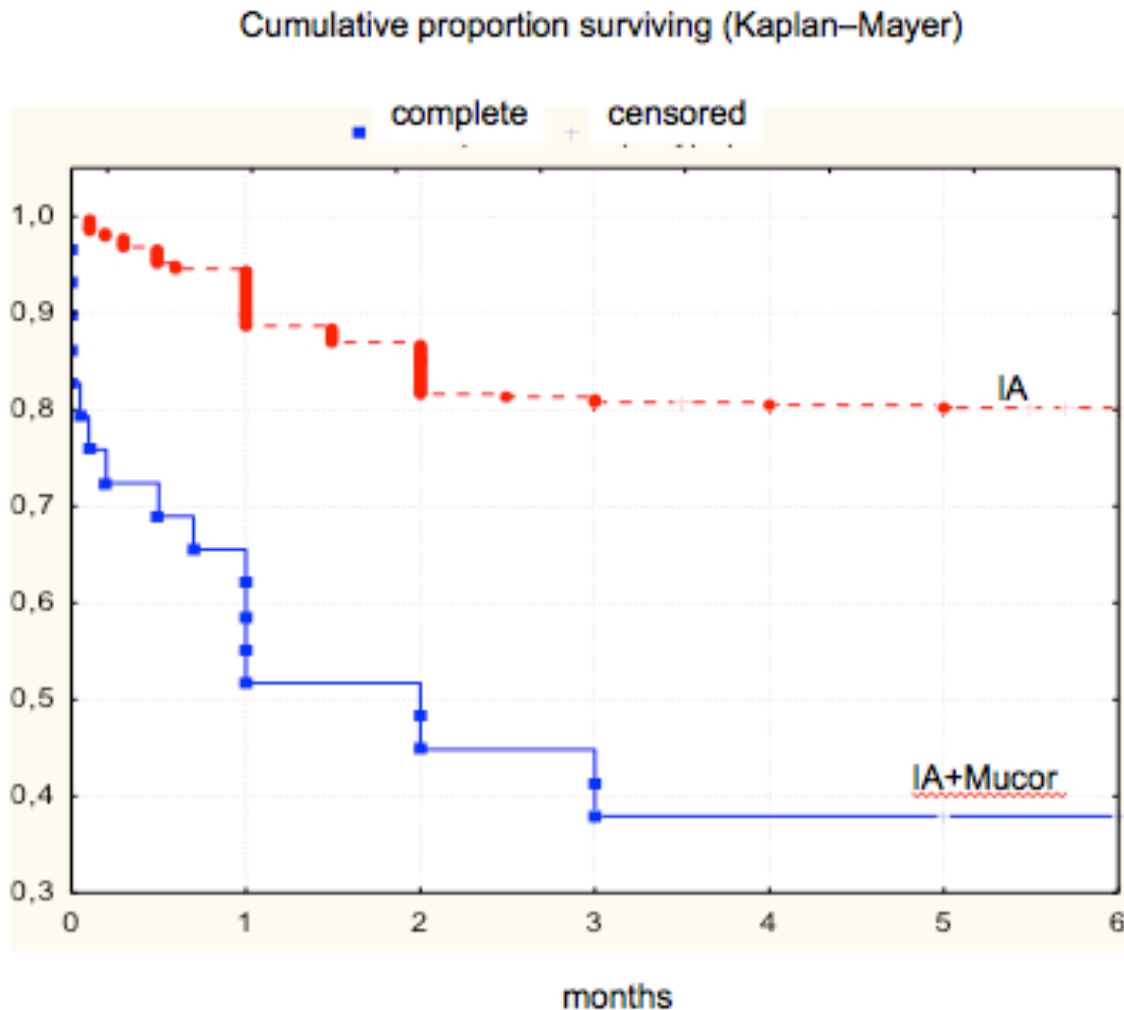
Invasive aspergillosis in Saint Petersburg, Russia overall survival rate (1998-2016, n=645)



- favorable prognosis factors: early bronchoscopy, voriconazole use and secondary antifungal prophylaxis

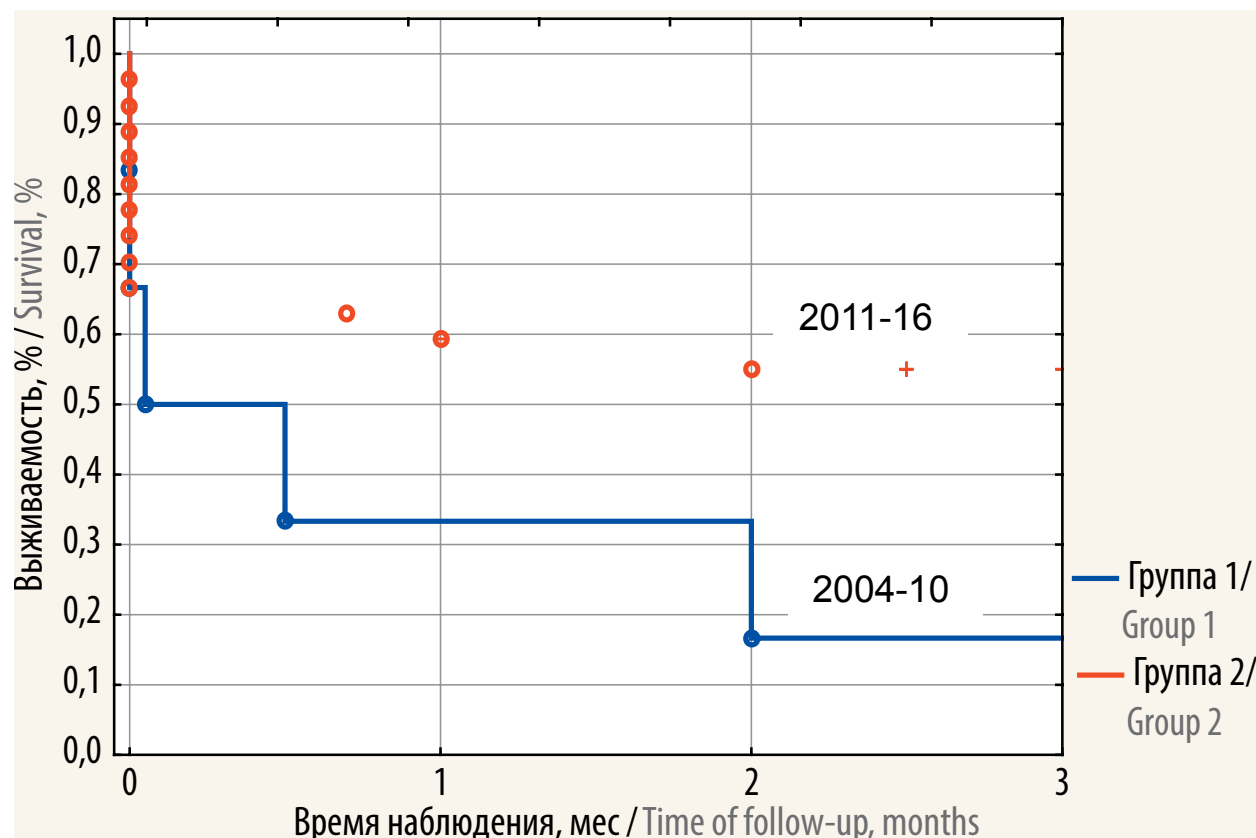
Mucormycosis vs Aspergillosis

overall survival rate (2007-17, n=512)



Mucormycosis in Saint Petersburg, Russia

overall survival rate (2004-10 vs 2011-16, n=59)



- Unfavorable prognosis factors: ≥ 2 organs involvement, unresolved neutropenia and hemoptysis, favorable – remission of underlying disease and combined antifungal therapy (lipid AmB + echinocandin)

Contrasts between mucormycosis and aspergillosis in leukemia

- severe immunosuppressed patients, often after invasive aspergillosis
- paranasal sinuses involvement, frequently disseminated
- typical clinical feature – hemoptysis, lung CT scan – pleural effusion, lesions with destruction, and a "reverse halo" sign
- difficult diagnosis
- liposomal AmB (in combination with echinocandin)
- surgery
- IFD is not a contraindication for allo-SCT

Acknowledgment

Kashkin Research Institute of Medical Mycology
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Transplantation, Pavlov 1st St Petersburg State Medical University

Petrov Research Institute of Oncology

Almazov Federal Medical Research Center

Russian Research Institute of Hematology and Transfusion

Clinical Scientific and Practical Cancer Center

Children's Hospital №1

City Hospital №15

City Clinical Hospital №31

Leningrad Regional Clinical Hospital