

Laboratorijska dijagnostika invazivnih gljivičnih infekcija -prezentacija vodiča-

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Qol

Grant : Pfizer

Advisory board: Pfizer
MSD
Astellas
Gilead

Predavanja: Pfizer
MSD
Astellas
Gilead

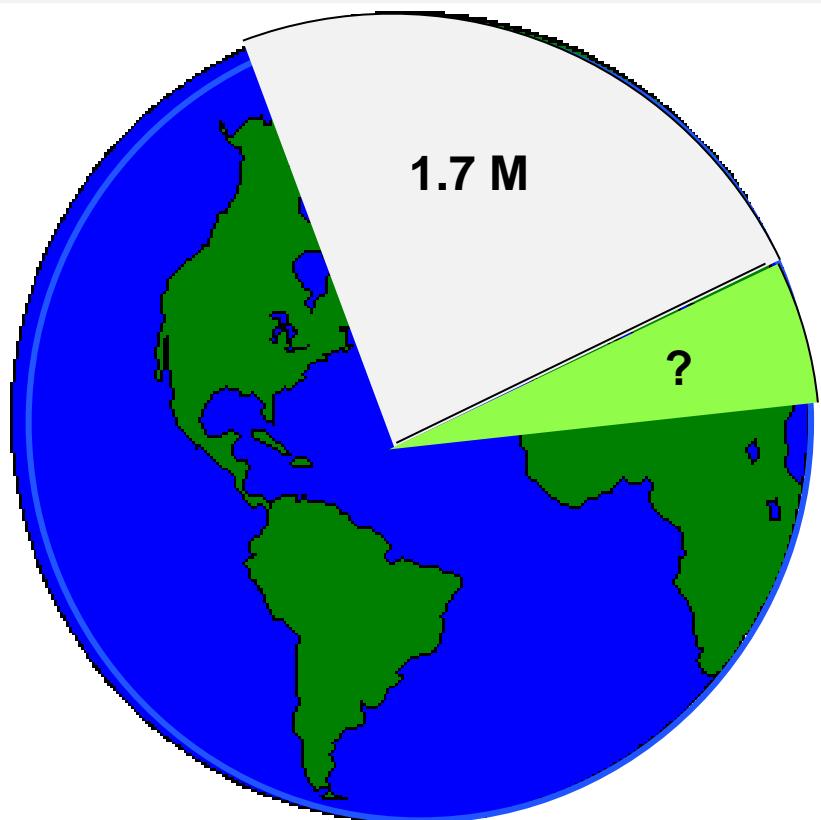
Gljivične infekcije – globalni problem

svetska populacija ~7 milijardi

Visoka
PREVALENCIJA

POVRSNE - 1.7 MILIJARDA

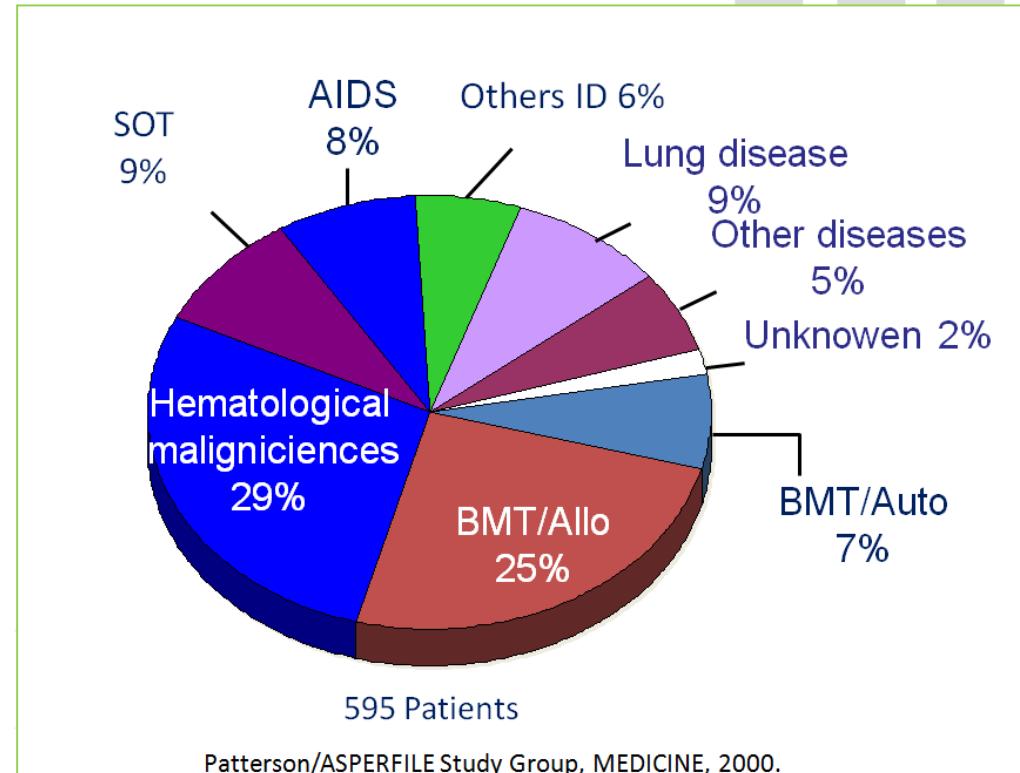
mortalitet 0%



Visok
MORTALITET

INVAZIVNE ???

mortalitet ~ 1,5 milion / godisnje



Invazivne gljivične infekcije u Srbiji

Size of population at risk for selected serious fungal diseases (SFD) in Serbia		
Asthma	311,806	4.42
COPD	250,302	3.55
*Cancer – lung	7,260	1.02
Sarcoidosis	1,120	0.16
CF in adult	65	0.00092
AML	212	0.003
Allogenic SCT	50	0.00071
SOT	59	0.00084
*HIV not under ART	244	0.00346
*Tuberculosis pulmonary	898	0.01272

***Total cases in 2016:** Cancer 42,221 (0.167%); HIV 2441 (0.035%); TB 962 (0.0136%)

Abbreviations: SCT – solid organ transplant; ART-anti retroviral therapy; CF-cystic fibrosis; AML- Acute myeloid leukemia; COPD-chronic obstructive pulmonary disease, RS-rhinosinusitis, CF-cystic fibrosis, FK-fungal keratitis, TC-tinea capitis , RVVC- recurrent vulvovaginal candidiasis, OM- onychomycosis , y-years;

Source: <http://webrzs.stat.gov.rs/WebSite/Public/PageView.aspx?pKey=162>

Invazivne gljivične infekcije u Srbiji

Table 2. Yearly incidence estimated for serious fungal diseases in Serbia: population in 2016.

Disease	Number of infections per underlying disorder per year					Rate/ 100.000	Total burden
	None	HIV/ AIDS	Respiratory	Cancer/ chemotherapy	ICU		
Oesophageal candidiasis	-	42	-	131	-	2.4	173
Candidaemia	-	-	-	50	468	7.3	518
<i>Candida</i> peritonitis	-	-	-	-	187 [#]	2.7	187
Recurrent vaginal candidiasis (4x/year+)	135,303	-	-	-	-	3,737 ^{##}	135,303
Allergic bronchopulmonary aspergillosis	-	-	9,094	-	-	129	9,094
Severe asthma with fungal sensitization	-	-	10,393	-	-	147	10,393
Chronic pulmonary aspergillosis ^a	-	-	448	-	-	6.4	448
Invasive aspergillosis ^b	-	-	478	41	100	8.8	619
Mucormycosis, <i>Fusarium</i>	-	-	-	20	3	0.33	23
Cryptococcal meningitis	-	5	-	-	-	0.07	5
<i>Pneumocystis</i> pneumonia	-	15	-	2	45	0.88	62
Total burden estimated	135,303	61	20,413	245	821	2,221	156,825



OUR VISION IS TO REDUCE ILLNESS AND DEATH
ASSOCIATED WITH FUNGAL DISEASES WORLDWIDE.



LEADING
INTERNATIONAL
FUNGAL
EDUCATION

Over 1 million eyes go blind
each year because of fungal
keratitis

Antifungal therapy for fungal
keratitis is **60-75%**
effective in saving sight

Over **400,000** people
develop Pneumocystis
pneumonia and always die
without therapy

High dose cotrim therapy is
available, cheap and effective

Nearly a **BILLION**
people have a Fungal
Infection of the skin, the 4th
most common illness on
earth, after headaches and
dental caries

Pravovremena i tačna laboratorijska diagnostika

DOKAZANE

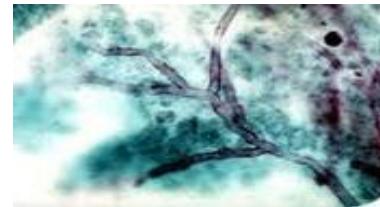
VEROVATNE

Metode: dokazane / verovatne GI

Citologija

BRZA, JEFTINA, DOKAZUJE SVE GLJIVE

Niska senzitivnost
Invazivne procedure uzorkovanja
Neophodan ekspert za detekciju gljiva
Neophodna strucna interpretacija nalaza



Kultura

JEFTINA, IZOLUJE SVE GLJIVE

MOGUĆ ANTIMIKOGRAM I IDENTIFIKACIJA
Spora metoda, niska senzitivnost,
Invazivne procedure uzorkovanja

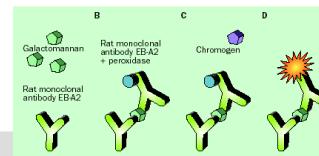


Ag/At

BRZA, VISOKA SENZITIVNOST

VISOKA PPV (At) VISOKA NPV (Ag)

Interpretacija???

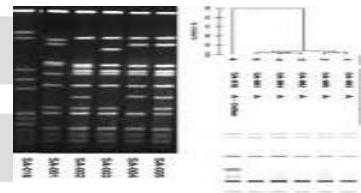


PCR

BRZA, VISOKA SENZITIVNOST

Kontaminacija???, Interpretacija???

Invazivno uzorkovanje???



Prevalencija - *Aspergillus*

Poster Presentations

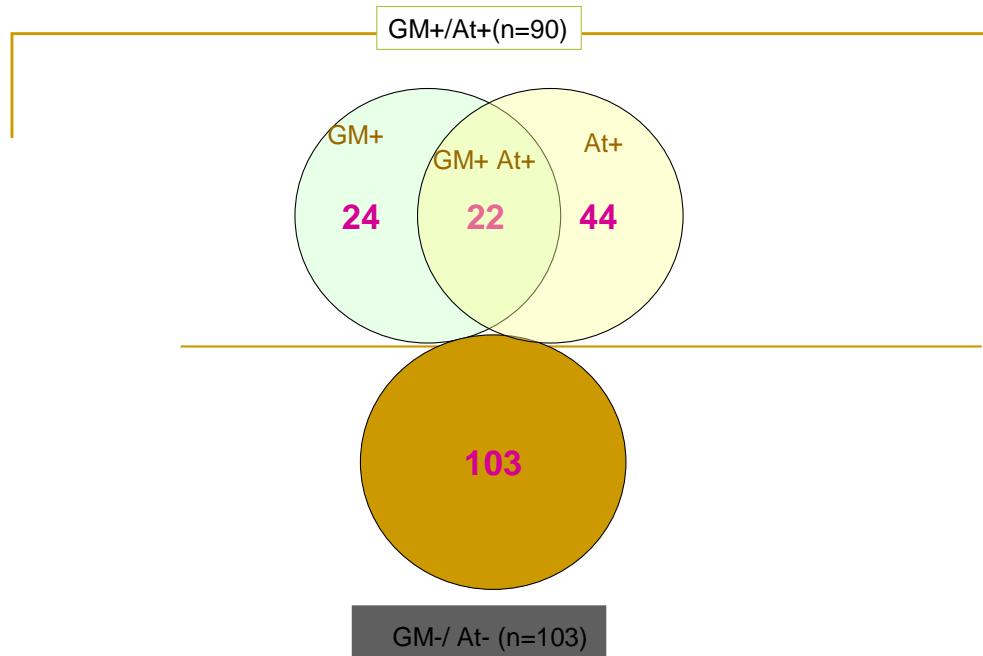
P154

Screening for galactomannan and anti-*Aspergillus* antibodies in haematological patients suspected for developing invasive aspergillosis

E. Ratkov¹, A. Vidovic², N. Suvajdzic Vukovic², A. Dzamic¹ and V. Arsic Arsenijevic¹

¹Institute of Microbiology and Immunology, Belgrade, Serbia,

²Institute of Hematology, Clinical Center of Serbia, Belgrade, Serbia



Prevalencija - *Candida*

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ORIGINAL ARTICLE



Candida bloodstream infections in Serbia: First multicentre report of a national prospective observational survey in intensive care units

Valentina Arsić Arsenijević¹ | Suzana Otašević² | Dragana Janić³ | Predrag Minić⁴ |

Jovan Matijašević⁵ | Deana Medić⁶ | Ivanka Savić⁷ | Snežana Delić⁸ |

Suzana Nestorović Laban⁹ | Zorica Vasiljević¹⁰ | Mirjana Hadnadjev¹¹

						Spp.	antifungals	R	S-DD	Outcome
						FCA		ITR	FLU	Alive
						FCA		-		Alive
						FCA		-		Alive
						FCA		-		Alive
						FCA		ITR	VOR	Dead
						FCA		ITR	VOR	Dead
						FCA/APH/CAS/VOR		-	ITR/FCA	Dead
						FCA		-		Alive
						FCA		ITR		Alive
						ITR		-	ITR	Dead
						FCA		-		Alive
						/		FCY	ITR	Dead
						APH		-		Alive
						Ca	APH	-		Alive
						Cp	FCA/CAS/VOR	ITR		Alive
						Ca	FCA	-		Alive
						Ca	/	-		Alive
	CVD (n=4)									
	P01	IPD	54	M	Dilated cardiomyopathy	Ca	/	-		Dead
	P02	IPD	21	M	Intracranial haemorrhage	Cp	/	-	ITR	Alive
	P10	CCV	68	M	Cerebral artery aneurysm	Cp	FCA	-		Alive
	P25	IPD	78	F	Cardiomyopathy	Cp	/	-	ITR	Dead
	DM (n=5)									
	R02	CCN	83	M	DM, respiratory insufficiency, haemodialysis	Ca	APH	-		Alive
	R04	CCN	50	M	DM, respiratory insufficiency, malnutrition	Ca	APH	-		Alive
	R06	CCN	49	F	DM, pancreatitis, biliary calculus	Clus	APH	-		Alive
	R07	CCN	59	M	DM, thrombophlebitis	Ca	APH	ITR	VOR	Alive

Candida - the most common fungal pathogens in our patient population

Prevalencija – retke gljive

What lurks in the sellar?

Sandra Pešić, Valentina Arsić Arsenijević, Milica Skender Gazić, Toplica Milojević, Ivica Pendjer, Marko Stojanović, Vera Popović

Lancet 2010; 375: 432

Neuroendocrine Unit, Institute of Endocrinology (S Pešić MD, M Stojanović MD, Prof V Popović MD), Institute of Neurosurgery (T Milojević MD),

Institute of Otorhinolaryngology (I Pendjer MD), University Clinical Center, Belgrade, Serbia; Reference Medical Mycology Laboratory, Institute of Microbiology, Belgrade, Serbia (V A Arsenijević MD); and Institute of Pathology, School of Medicine University of Belgrade, Belgrade, Serbia (M S Gazić MD)

Correspondence to: Prof Vera Popović, Institute of Endocrinology, Dr Subotica 13, 11000, Belgrade, Serbia popver@unibz.ac.rs

In June, 2008, a 44-year-old immunocompetent man presented to us with sinusitis associated with headache, transient diplopia, and dizziness. He had a 7-year history of chronic sinusitis occasionally treated with pseudoephedrine and antibiotics. CT of the sinuses showed opacification of the paranasal sinuses which were filled with thick, dark, mucinous material consistent with the enhanced

functional endoscopic sinus surgery was done. The patient was treated with systemic antimycotics (liposomal amphotericin B, 2 weeks before and 1 week after surgery) and systemic and topical corticosteroids, followed by itraconazole for 2 months). When seen in August, 2009, he had improved clinically and prolactin concentration had

Advanced to CCN 2010

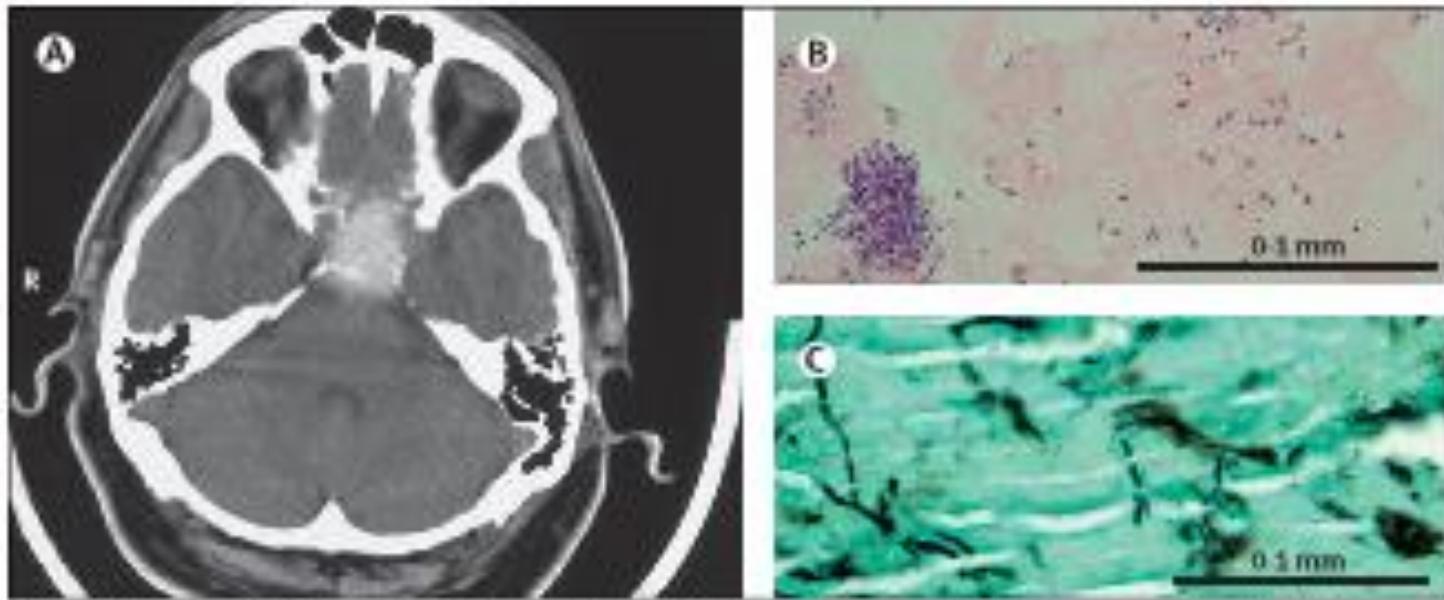
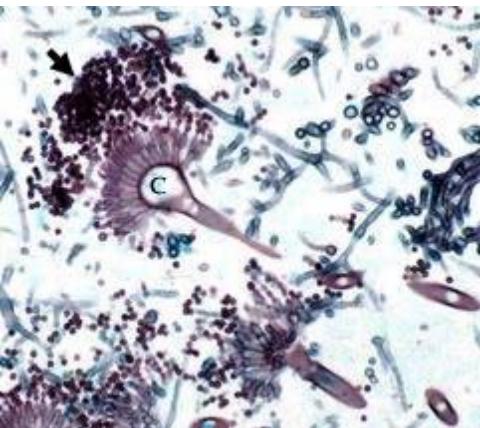


Figure: CT and histology of sellar contents obtained at surgery

(A) Sellar mass and bony erosion. (B) Extracellular mucin with eosinophil clusters and debris (H&E staining $\times 400$). (C) Septate, branched fungal hyphae (Grocott staining $\times 400$).

NRL UM strategija – kombinacija 3 testa



citologija



kultura

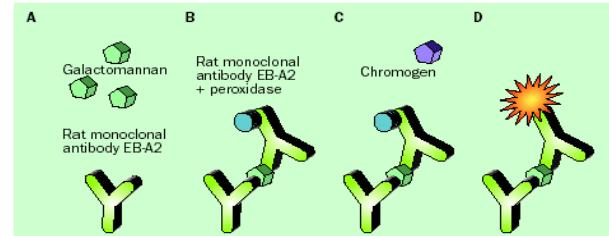
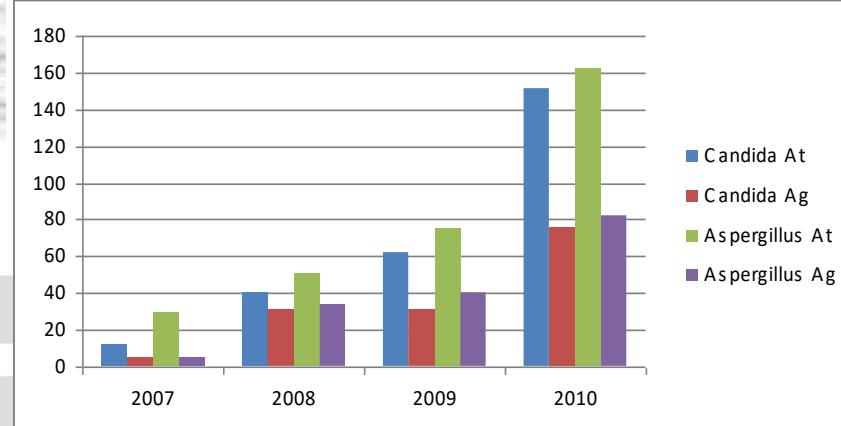


Figure 1. The Platelia Aspergillus ELISA technique. A serum ratio is calculated by dividing the optical density of the patient's serum sample by the mean optical density of two threshold control samples that contain 1 µg/L of galactomannan.

Biomarkeri



Dijagnostičke metode IGI – NRL UM

Biomarkeri gljiva galactomannan-GM i mannan-MN

Antitela pacijenta: anti-*Candida* I anti-*Aspergillus*

+

✓ Citologija

✓ Kultura

Kumulativna senzitivnost je veća kada se kombinuju biomarkeri;

+

Neočekivane gljive – dokazujemo citologijom/kulturom
Nivo: dokazana IGI
identifikacija i antimikogram



Vodič za dijagnozu i terapiju invazivnih glijičnih infekcija

Valentina Arsić Arsenijević
Dražana Janić

DIJAGNOSTIČKO-KLINIČKA MIKOLOGIJA

DOKAZIVANJE GLJIVA PRIMENOM METODA CITOLOGIJE I DIJAGNOZA INVAZIVNIH GLJIVIČNIH INFEKCIJA

DOKAZIVANJE GLJIVA PRIMENOM METODA IZLOVANJA PREDIKCIJA I DIJAGNOZA INVAZIVNIH GLJIVIČNIH INFEKCIJA

IZOLATI GLJIVA: ANTIMIKOGRAM, IDENTIFIKACIJA I TIPIZACIJA

DOKAZIVANJE BIOMARKERA GLJIVA - ANTIGENA I DIJAGNOZA INVAZIVNIH GLJIVIČNIH INFEKCIJA

DOKAZIVANJE BIOMARKERA PACIJENATA - ANTITELA

PRAĆENJE I DIJAGNOZU INVAZIVNIH GLJIVIČNIH INF.

DOKAZIVANJE NUKLEINSKIH KISELINA GLJIVA

DIJAGNOZA INVAZIVNIH GLJIVIČNIH INFECIJA

CIL VODIČ 2013;
SCMID VODIČ 2012;
ORTC-MSG DEFINICIJE 2008;
USA *Candida*, 2018,
USA *Aspergillus*, 2018

PRIMENA-DOZIRANJE ANTIMIKOTIKA

TERAPIJA I PREVENCIJA INVAZIVNIH GLJIVIČNIH INFEKCIJA

PRIMENA-DOZIRANJE ANTIMIKOTIKA PEDIJATRIJA-NEONATOLOGIJA

PREVENCJIU I TERAPIJU INVAZIVNIH GLUVIČNIH INFKECIJA

DIAGNOZA I TERAPIJA *Pneumocystis jiroveci* PNEUMONIJE

PREPORUKE I DOPUNE IZ VODIČA ZA INVAZIVNE GLIVIČNE INFKECJUE

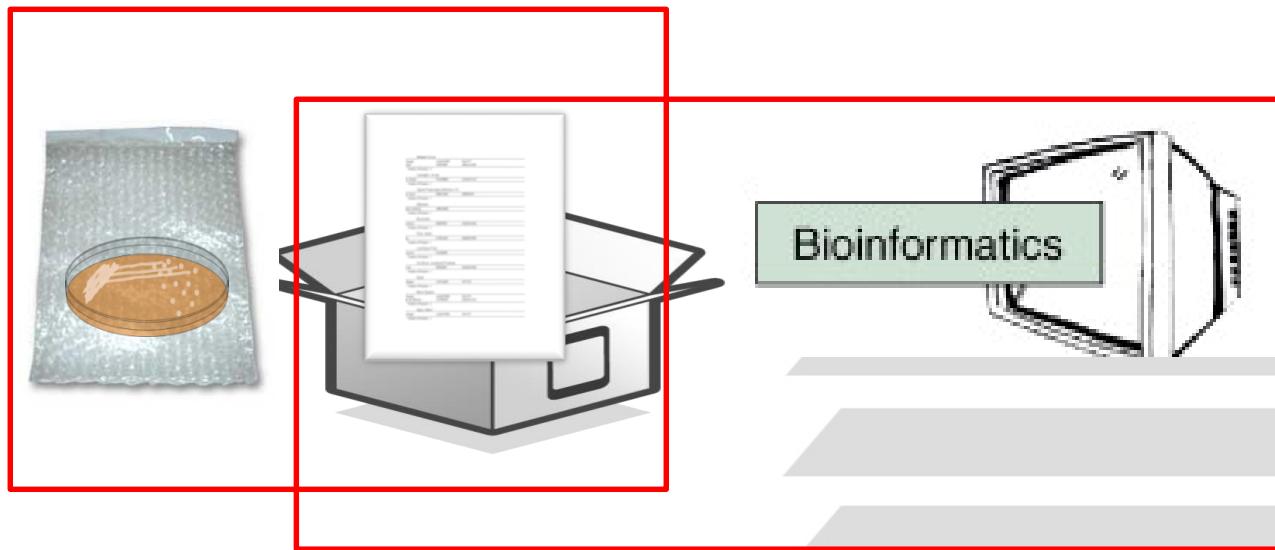
FORMIRANJE REGISTRA PACIJENATA, BANKE UZORAKA I KOLEKCIJE KLINIČKIH IZOLATA GLIIVA

ECIL recommendations for the use of biological markers for the diagnosis of invasive fungal diseases in leukemic patients and hematopoietic SCT recipients.

Cilj – testovi za pravilno uzorkovanje i rano dokazivanje gljivija MYCOPACK

THE MORE YOU LOOK AT IT,
THE MORE PATIENTS YOU CAN SEE!

Self screening OR point of impact testing





Invazivne gljivične infekcije u Srbiji

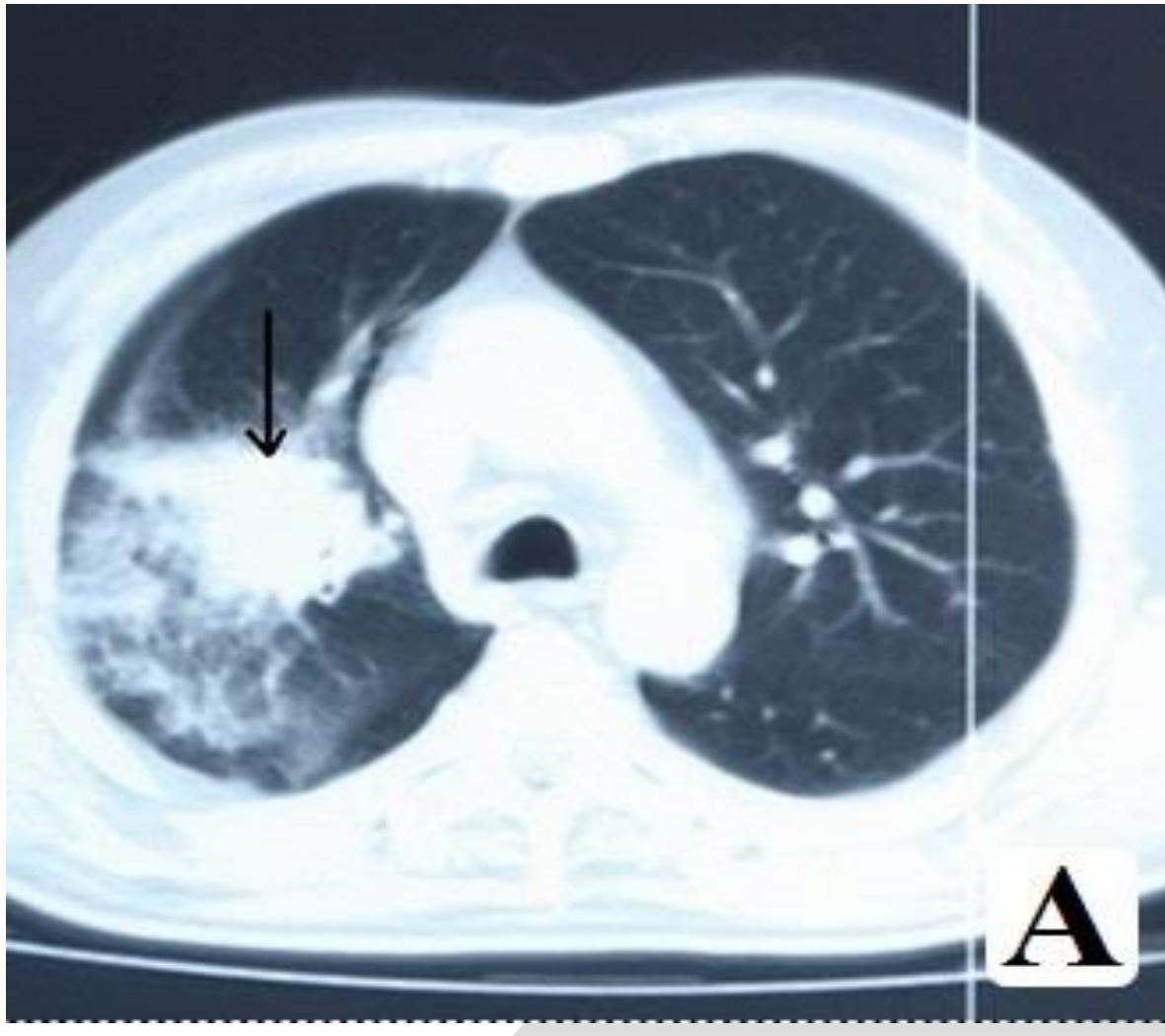


Invazivne gljivične infekcije u Srbiji

Slučaj 1

O pacijentu (deo I)

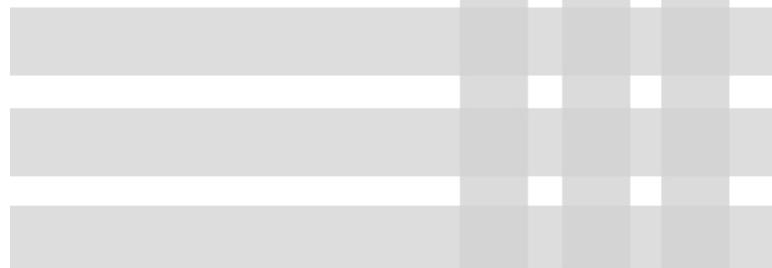
- **Mart 2011:** 52 godine star muškarac sa acute myeloblastic leukemia (AML)
- Hemoterapija “3+7” scheme
- Nastupa postinduciona aplazija koštane srži 4-og dana Th
- X-snimak pluća – normalan nalaz
- klinički pneumonija
- Meropenem i caspofungin uključeni
- Galactomannan GM nisko pozitivan (index 0.55)
- Kontrolni X-snimak pluća: homogeno zamućenje gore desno: ukazuje na focalnu pneumoniju
- Bronhoskopija: citološki nalaz hifa plesni



A: Mart 2011, CT

CT: konsolidacione promene u mekom tkivu alveola

Prelimarna Dg?
Th?



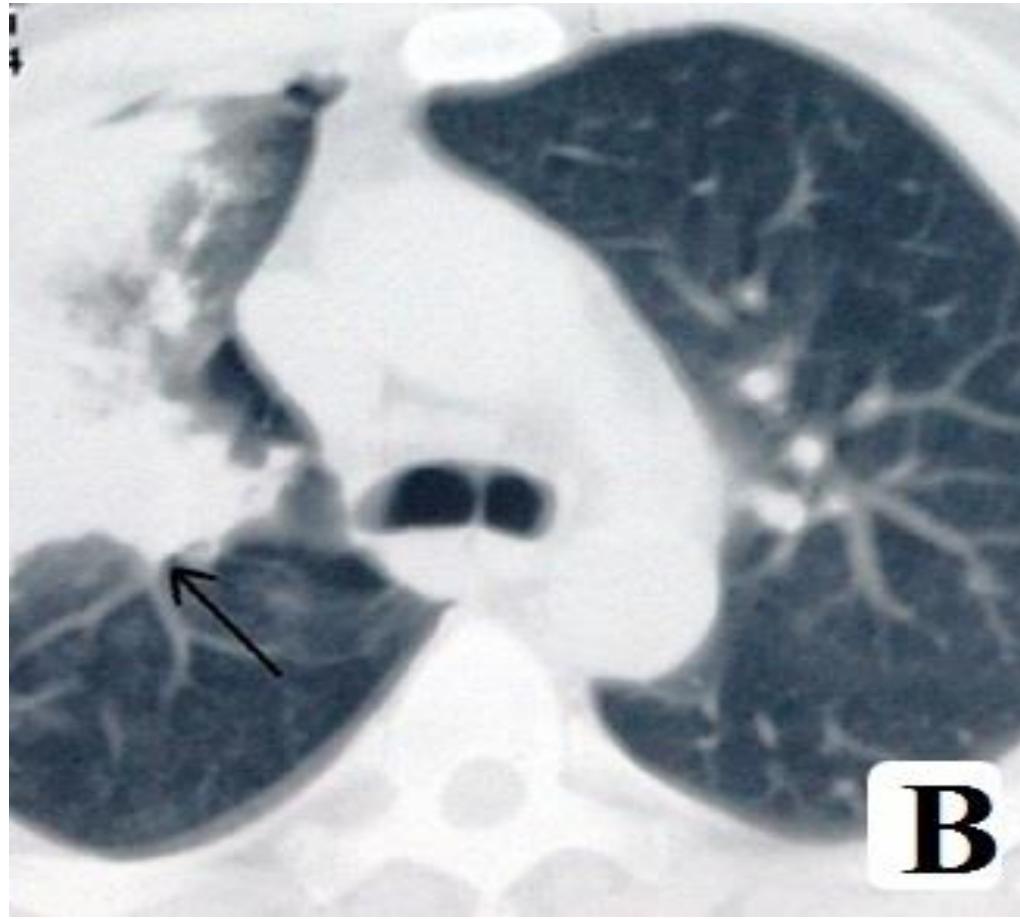
Odgovor 1

Invasive pulmonary aspergillosis;
Voriconazole;

O pacijentu (nastavak)

- Maj 2011: normalna KS, afebrilan
- Re-indukcija hemoterapije i voriconazole
- 5 dana hemoterapije febrilnost
- CT toraksa pokazuje promene svih bronhijalnih segmenata, interlobularno, nodularna zamućenja, suspektna masa u lumenu v. cava superior, v. cava inferior, v. azygos and v. lienalis
- GM nisko pozitivan
- Bronchoskopija:

citološki videne neseptirane hife

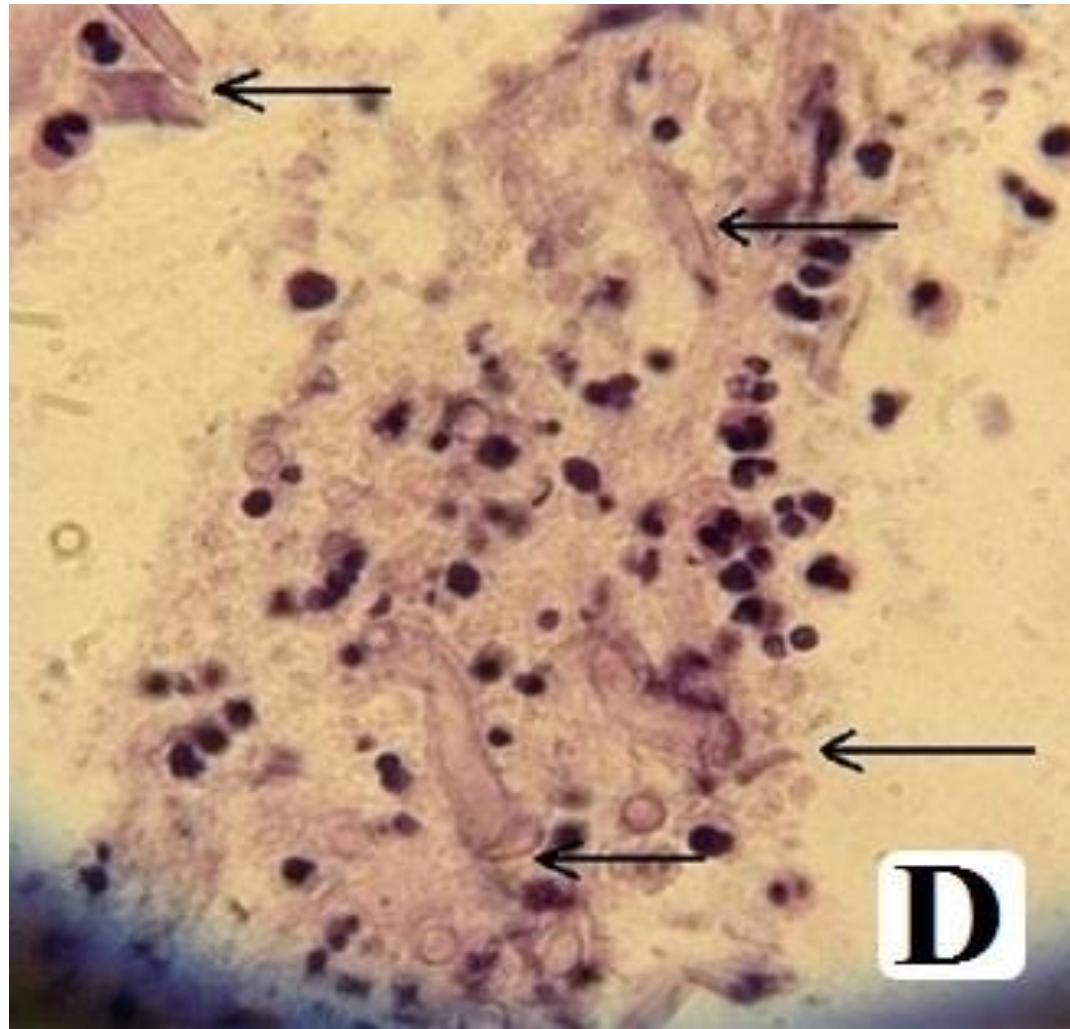


(B) – Maj 2011, CT

CT: peribronchial circular thickening, deformation and constriction of all bronchial segments, peribronchial propagation, interlobular septal and nodular opacities, suspected clot masses in the lumen of the v.cava superior, v. cava inferior, v. azygos and v. lienalis)



(C) – May 2011, multi-slice thoracic CT
CT the signs of minor regression of the soft tissue
inflammatory consolidation



(D) – Maj 2011, biopsija plućnog tkiva

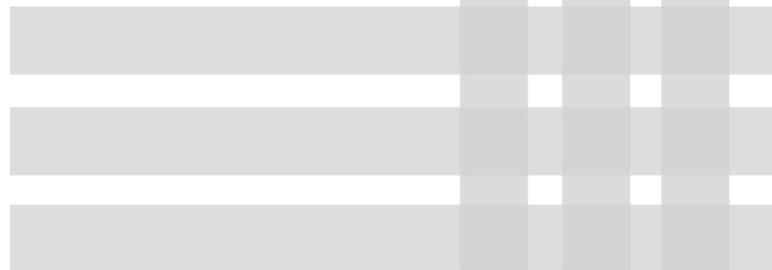
Citologija: neseptirane hife

Hematoxilin & Eosin staining x 400)

Pitanje 2

Definitivna Dg?

Th?

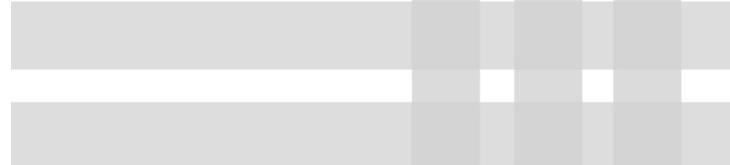


Pitanje???

- A) Invasivna plućna aspergiloza/Vori
- B) Invasivna plućna mucormikoza/AmB
- C) Plućna tuberkuloza/Isoniasid
- D) Sarkoidoza/kortikosteroidi

Odgovor

- A) Invasivna plućna aspergiloza/Vori
- B) Invasivna plućna mucormikoza/AmB**
- C) Plućna tuberkuloza/Isoniasid
- D) Sarkoidoza/kortikosteroidi



[Proven invasive pulmonary mucormycosis successfully treated with amphotericin B and surgery in patient with acute myeloblastic leukemia: a case report.](#)

Vidovic A, Arsic-Arsenijevic et al J Med Case Rep. 2013 Dec 3;7:263



Invazivne gljivične infekcije u Srbiji

Slučaj 2

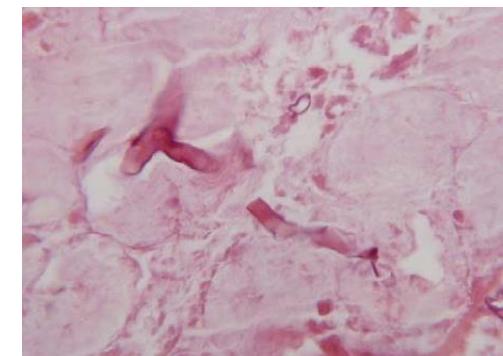
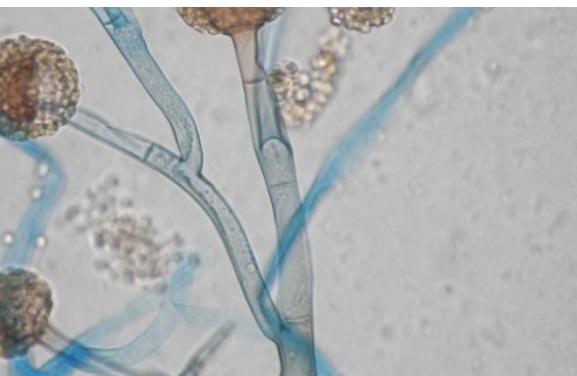
O pacijentu:

- April 2012**, 53 godine star muškarac, iz ruralnog područja sa tumorom ezofagusa (Ca Sqamocellulare);
- St. post. hemo-Th et radio Th,
- nastaje jatrogena aplazija koštane stži ($Le<1$, $Tr=58$, $HgB=110$)
- Th: Neupogen, Diflucan
- 15.04.2012.** slabost, suva usta, febrilnost
- 18.04.2012.** razvija se zapaljenje, crvenilo, hemoragične i nekrotične lezije u desnom zigomatičnom predelu lica, obe orbite i frontalni region
- X-zračenje pluća: infiltracije
- Aplazija koštane srži
- laboratorija: $HGB=110$, $Le=0.8$, $Tr=58$, $Urea=33.1$, $Creatinine=67$, total bilirubin=69.9, direct bilirubin =44.9, CRP =207, alkaline phosphatise =150, gamma GT=117



O pacijentu (nastavak):

- 19.4.2012. progresivno pogoršanje opšteg stanja
- Hemoragične promene kože lica i nekroza mekog tkiva
- Desno oko - ceratoconjunctivitis ;
- Promene na oba oka i skoro celog lica
- Biopsija uzeta sa promena na licu
- Citološki – ne septirane hife



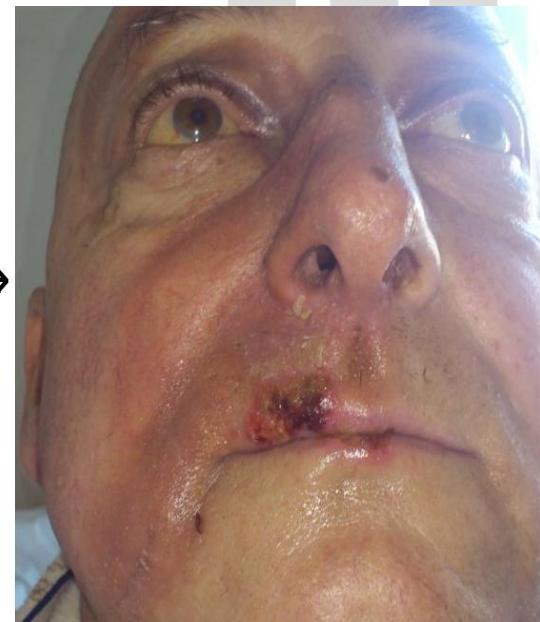
Pitanje 1

Dijagnoza?

Th AmB?



Th AmB

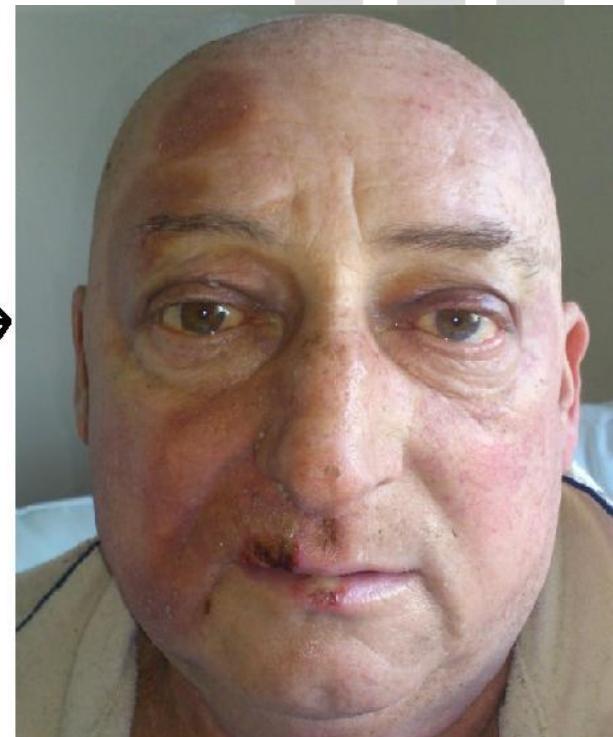
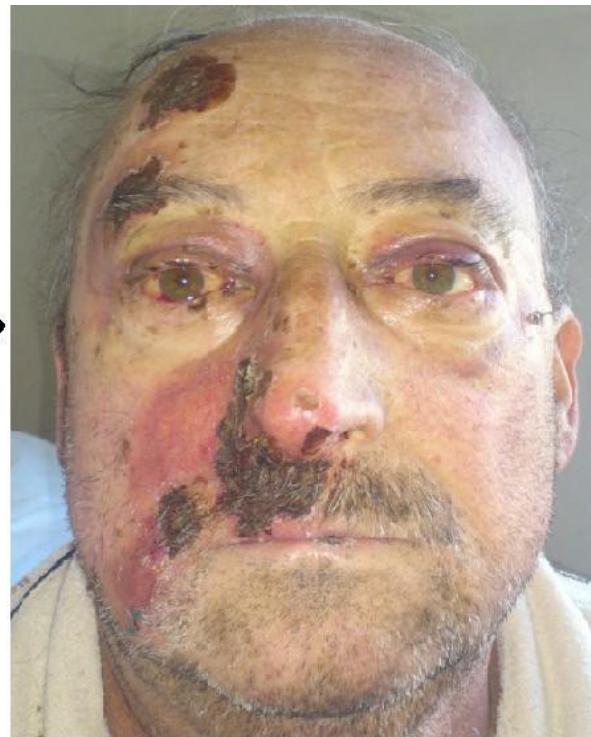


5. dan od početka Th Amfocil-om

7. dan od početka Th Amfocil-om

14. dan od početka Th Amfocil-om

Th AmB



Th AmB



5. dan od pocetka Th Amfocil-om

7. dan od pocetka Th Amfocil-om

14. dan od pocetka Th Amfocil-om

Pitanje?

- A) Invazivna aspergiloza
- B) Anthrax
- C) Fungus ball
- D) Mucormycosis/zygomycosis

Odgovor

- A) Invazivna aspergiloza
- B) Anthrax
- C) Fungus ball
- D) Mucormycosis/zygomycosis**



Invazivne gljivične infekcije u Srbiji

Slučaj 3

O pacijentu:

- Dete hematološki pacijent, Novi Sad
- Hickman kateter prisutan; febrilnost prisutna;
- Odstanjen kateter, kultivisan vrh katetera;
- Vrha katetera – kultura hialine plesni
- Hemokultura *Staphylococcus* spp koag. neg.
- Terapija vankomycin
- Lezije na kože - progresija
- Dermatolog - vasculitis cutis reactiva

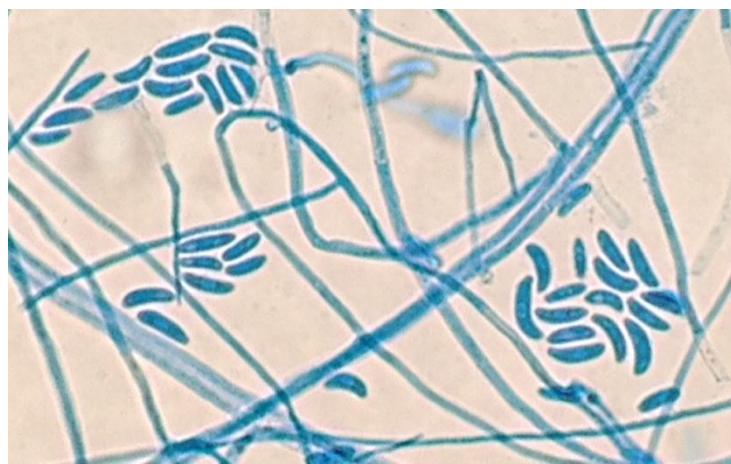
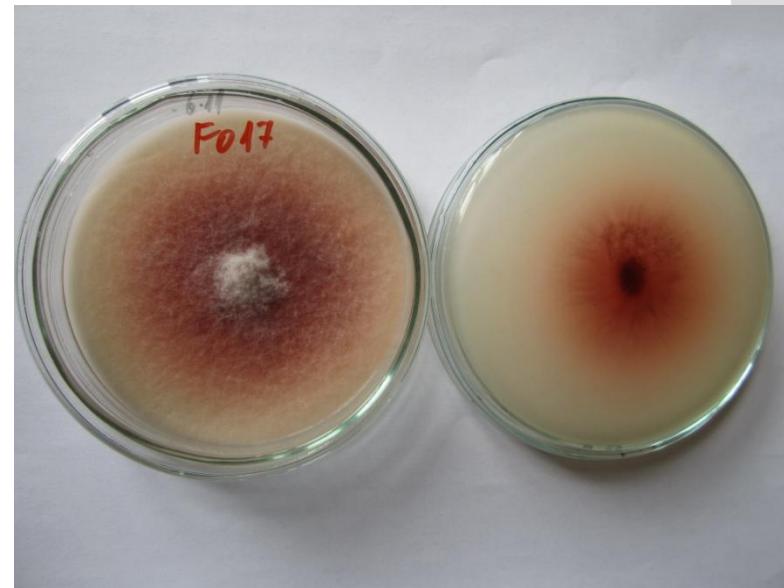
O pacijentu (nastavak):

- Hemokultura – hialine plesni
- GM pozitivan
- Anti-*Aspergillus* IgM pozitivan
- Terapija AmB
- Lezije na koži – regresija
- Pacijent – afebrilan
- Serija hemokultura - negativna





Hemokultura – hialine plesni



Pitanje???

- A) Bakteriemija
- B) Plućna aspergiloza
- C) *Candida* sepsa
- D) *Fusarium* sepsa

Odgovor

- A) Bakteriemija
- B) Plućna aspergiloza
- C) *Candida* sepsa
- D) *Fusarium* sepsa



Balkan Fungus 2018

First Balkan Conference
on Medical Mycology and Mycotoxicology



September 13-15, 2018
Timișoara - Romania

Hvala na pažnji!
Vidimo se u Temišvaru!

