



Dokazane, uobičajene, nove i retke ozbiljne gljivične infekcije kod pacijenata u Srbiji

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Qol

Grant : Pfizer

Advisory board: Pfizer
MSD
Astellas
Gilead

Predavanja: Pfizer
MSD
Astellas
Gilead

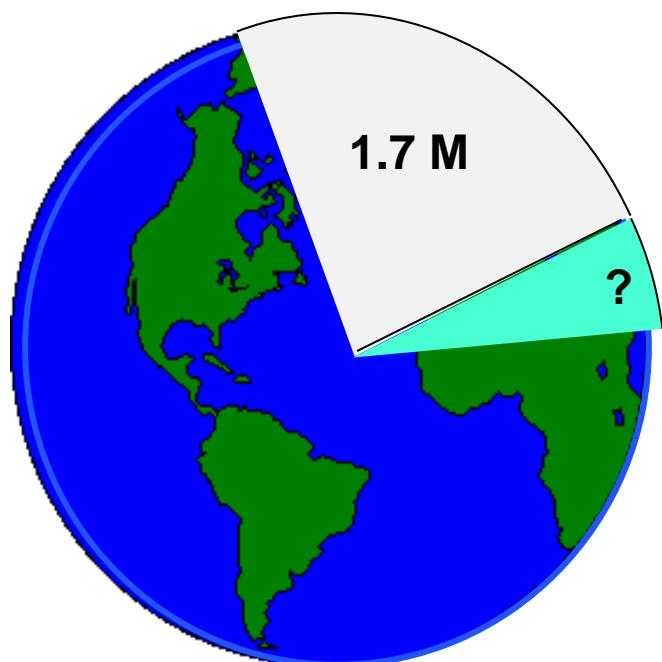
Gljivične infekcije – globalni problem

svetska populacija ~7 milijardi

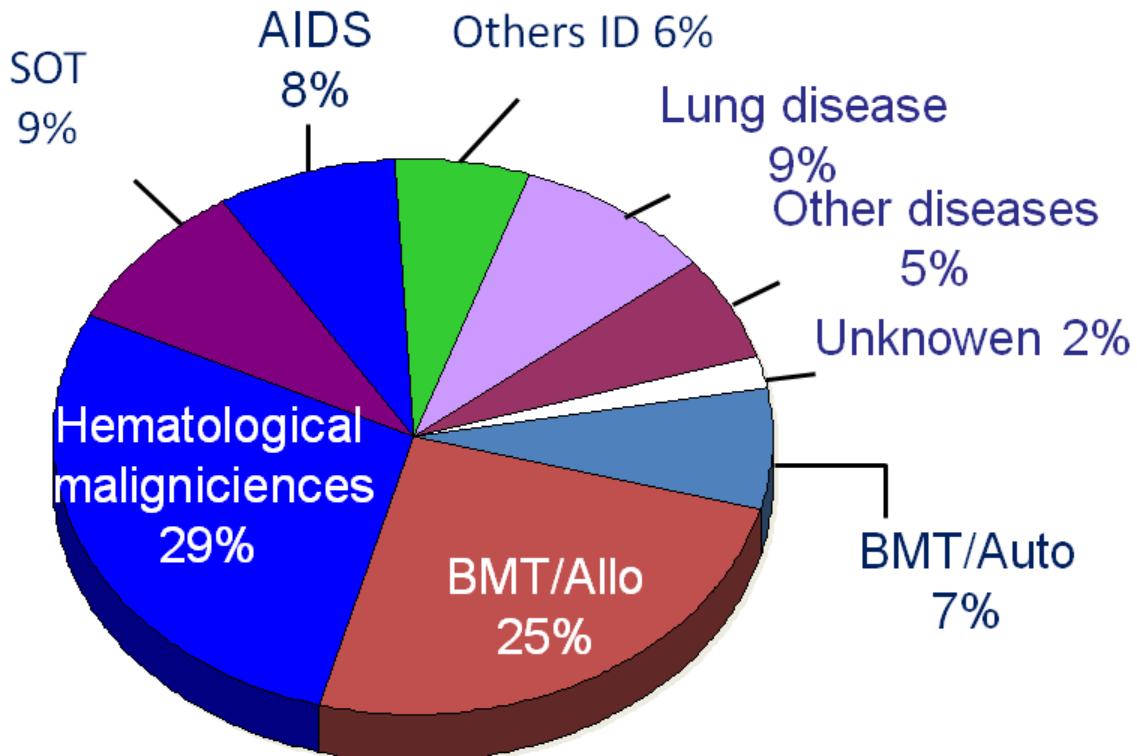
POVRSNE

INVAZIVNE ???

VISOKA PREVALENCIJA



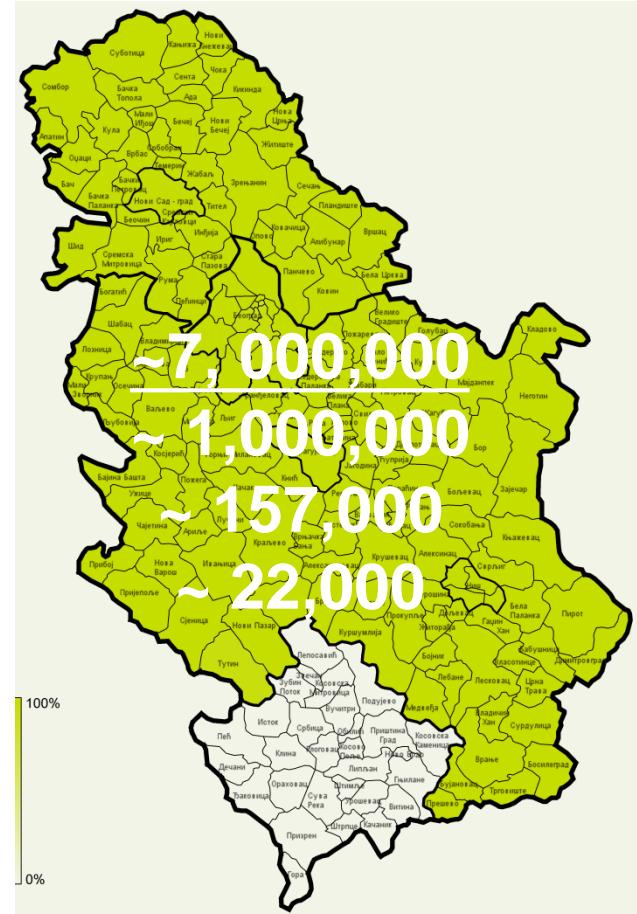
VISOK MORTALITET



mortalitet ~ 1,5 milion / godisnje

Title Estimated Burden of Serious Fungal Diseases in Serbia

Valentina Arsić Arsenijević ^{1,*}, David W Denning ²



~ 1,008,995 površne GI
~ 156,825 ozbiljne GI
~ 21,825 potencijalno fatalne GI

Table 1. Demographic characteristic and size of population at risk of serious fungal diseases in Serbia.

Population structure ^a	Number (n)	Percentage (%) of Total Population in Serbia
Total population	7,058,322	100
Adults (>15 y)	6,041,743	85.60
Adults (15-65 y)	4,688,795	66.43
Adults (>40 y)	3,850,802	54.56
Adults (>65 y)	1,352,948	19.17
Children (<14 y)*	1,016,579	14.40
Children (7-14 y)	544,632	7.72
Women (all ages)	3,620,692	51.30
Women (15-55 y)	1,804,043	25.59
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

*Source: <http://webrzs.stat.gov.rs/WebSite/Public/PageView.aspx?pKey=162>; Abbreviations: AML - Acute myeloid leukemia; ART-anti retroviral therapy; CF-cystic fibrosis; COPD-chronic obstructive pulmonary disease; FK-fungal keratitis; OM-onychomycosis; RVVC-recurrent vulvovaginal candidiasis; SCT-stem cell transplant; SOT-solid organ transplant; TC-tinea capitis; TB-tuberculosis, HIV-human immunodeficiency virus, y-years; OC, EC-oral, esophageal candidiasis. *Total cases in 2016: Cancer 42,221 (0.167%); HIV 2441 (0.035%); TB 962 (0.0136%); RVVC 135,303; OM 342,721; TC ~300; FK ~70; OC 208,489; EC 173.

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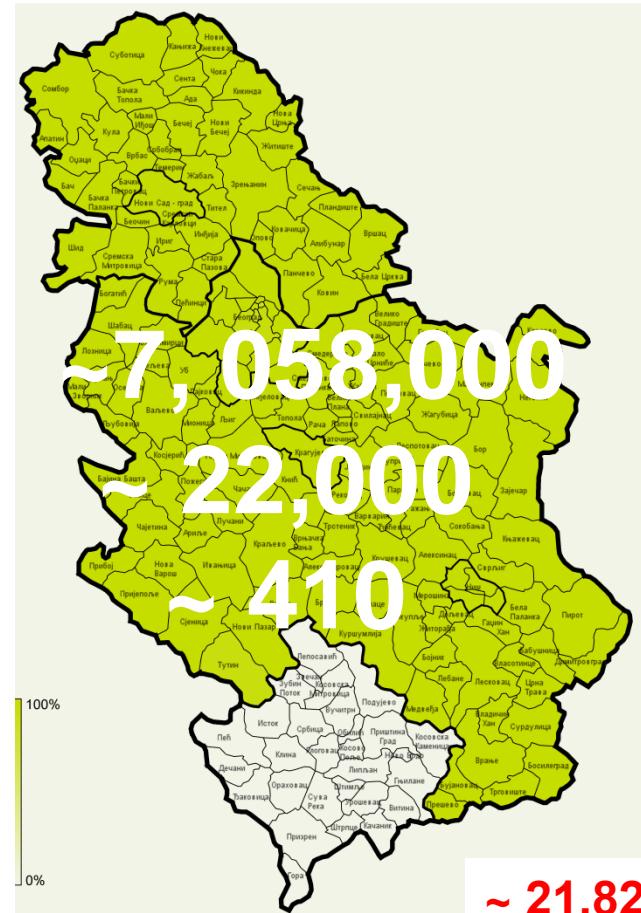


Table 2. Yearly incidence estimated for serious fungal diseases (SFD) in Serbia: population in 2016.

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 vulvovaginal candidiasis-RVVC (4x/year ^a)	135,303	-	-	-	-	3,737**	135,303
Allergic bronchopulmonary aspergillosis-ABRA	-	-	9,094	-	-	129	9,094
Severe asthma with fungal sensitization-SAFS	-	-	10,393	-	-	147	10,393
Chronic pulmonary aspergillosis-CPA ^a	-	-	448	-	-	6.4	448
Invasive aspergillosis IA ^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

^ainclude cases from abdominal surgery and peritoneal dialysis; ^binclude cases from pulmonary tuberculosis - PTB, chronic obstructive pulmonary disease - COPD, and sarcoidosis; ^b include cases from lung cancer, COPD, hematology malignancy - HM, and intensive care units - ICU; **All females as the denominator.

Aspergillus ~20,554
***Candida* ~878**
Retke gljive ~ 90

409 fatalne (5.79/100,000)

Dokumentovane, retke/preteče, duboke GI u Srbiji 2008-2017

Non-*Aspergillus* plesni:

Scedosporium apiospermum (Pseudallesheria boydii);
Fusarium proliferatum, F. oxysporum, F. Verticillides;

Aspergillus terreus;

Stachybotris chartarum;

Schizophyllum commune;

Mucorales

Non-*Candida* kvasnice:

Cryptococcus neoformans;

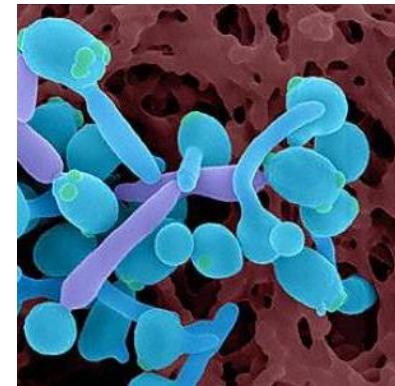
Geotrichum candidum;

Saccharomyces cerevisiae;

#Pneumocystis jirovecii

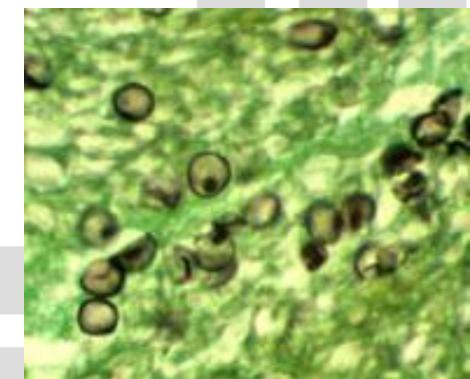
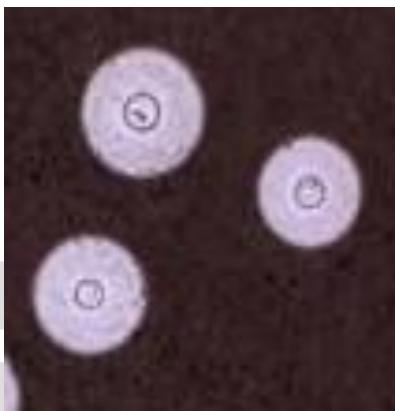
“Česte”: ~ 80%

Aspergillus i *Candida*

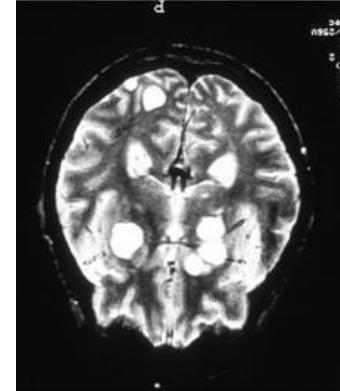
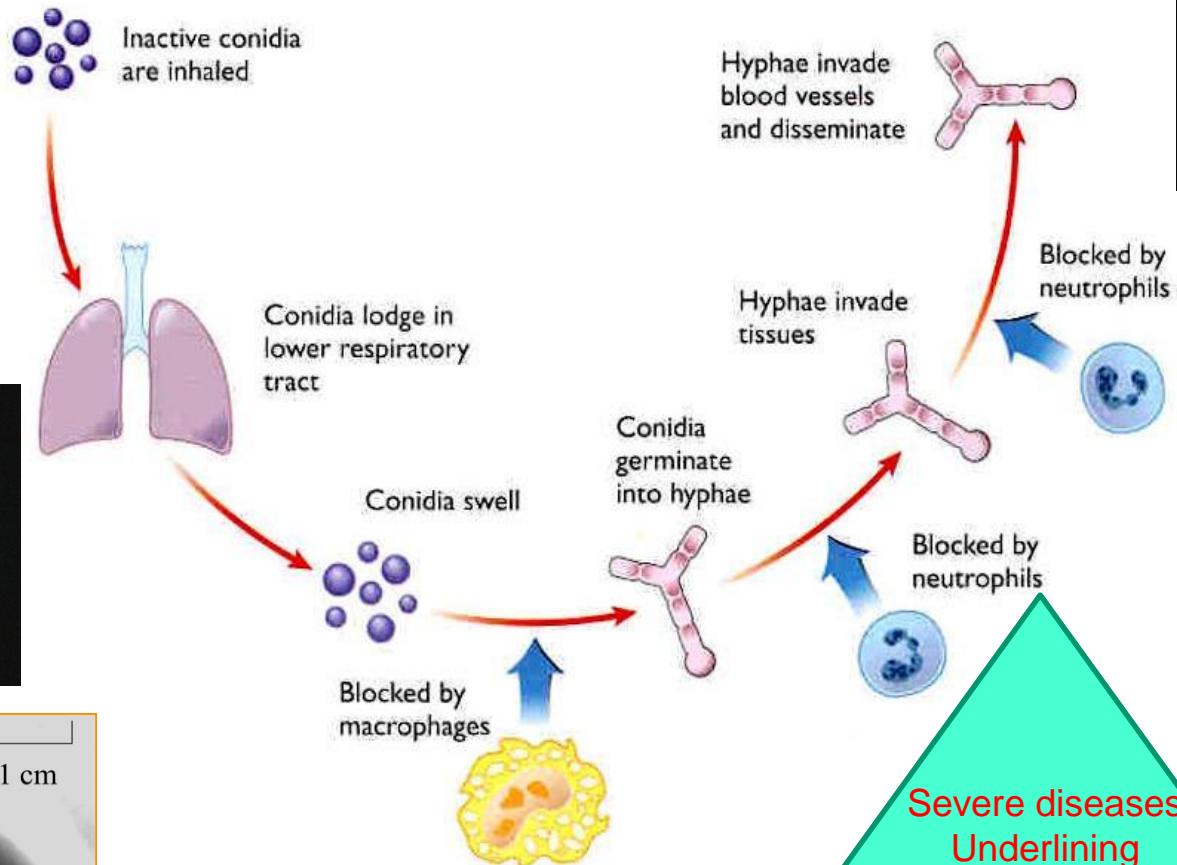
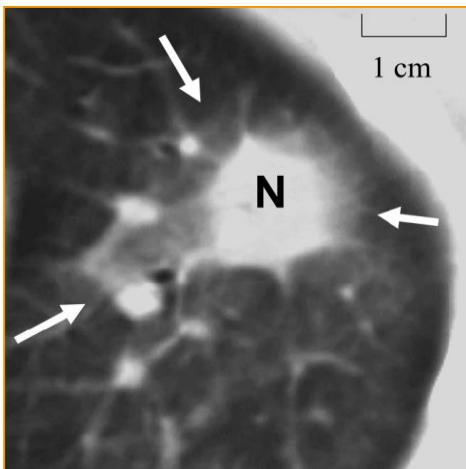
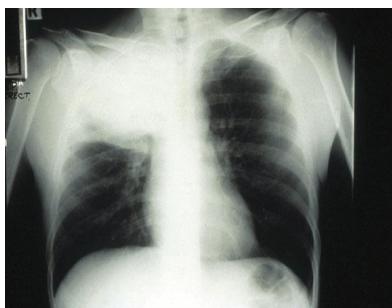


“Retke”: ~ 20%

Mucorales, *Fusarium*, *Cryptococcus*, *Pneumocystis*



Aspergillus i plesni



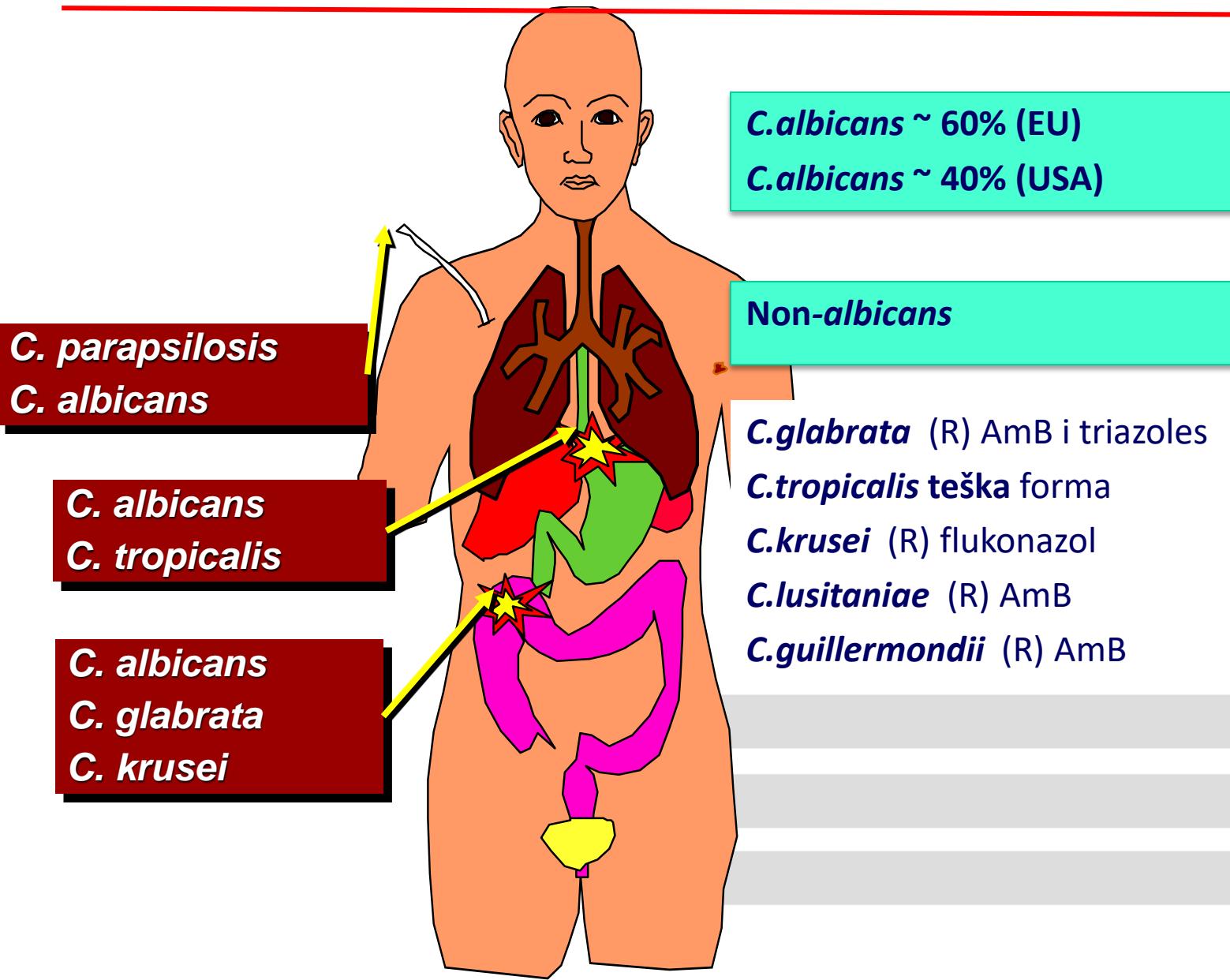
Severe diseases
Underlining disease

FUNGI
virulence
susceptibility
R - prim./sec.



TREATMENT
Time
Choice
Dozes

Candida i kvasnice



Uloga mikologa – dijagnoza

Molecular
Immunoassay
Culture

Screening

Confirmation
Diagnostic
Prognosis
Therapeutic

DOKAZANE

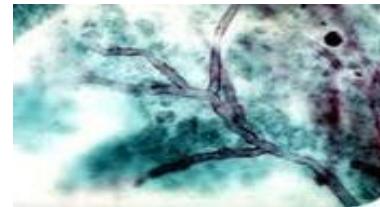
VEROVATNE

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

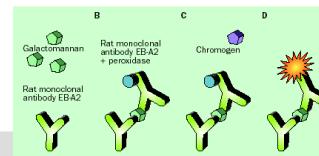


Ag/At

BRZA, VISOKA SENZITIVNOST

VISOKA PPV (At) VISOKA NPV (Ag)

Interpretacija???

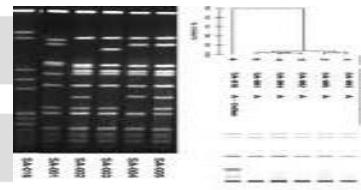


PCR

BRZA, VISOKA SENZITIVNOST

Kontaminacija???, Interpretacija???

Invazivno uzorkovanje???



Asperaillus

Poster Presentations

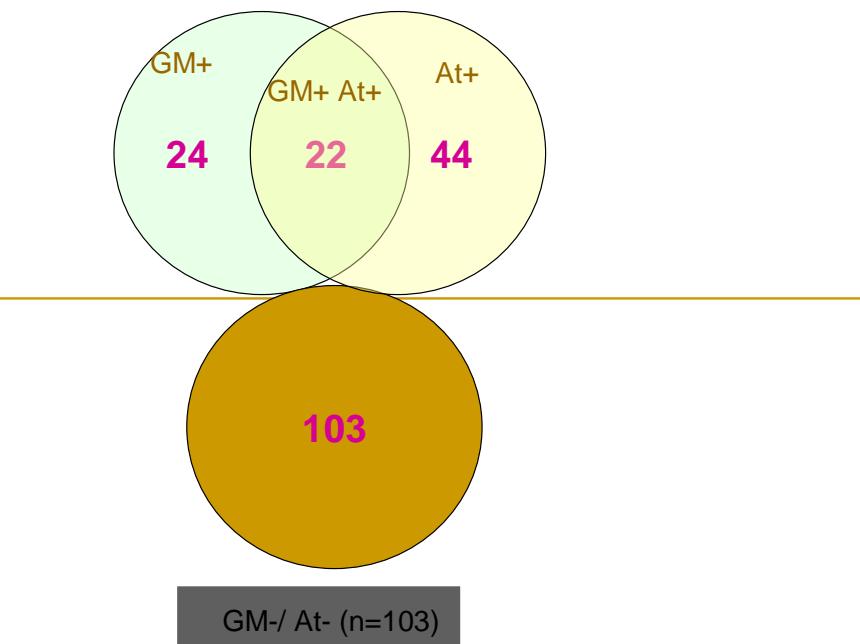
P154

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

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¹Institute of Microbiology and Immunology, Belgrade, Serbia,

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



Candida

and Groups	Institution	Age	Gender	Disease/Condition	Spp.	antifungals	R	S-DD	Outcome
NEONATES (n=9)									
P06 ^a	UCH	0	M	Diaphragmal hernia	Ca	FCA	-	ITR	Alive
P09 ^a	CCNp	0	M	LBW	Ca	FCA	-	-	Alive
P13 ^a	UCH	0	F	Left heart hypoplasia	Ca	FCA	-	-	Alive
R01 ^a	CCNp	0	M	LBW	Cip	FCA	-	-	Alive
P28 ^a	UCH	0	M	LBW	Ca	FCA	-	ITR	Dead
P17 ^a	CCNp	0	F	LBW	Ca	FCA	-	ITR	Dead
P23 ^a	IMC	0	M	Respiratory insufficiency	Ct	FCA/APH/CAF/VOR	-	ITR/FCA	Dead
P22 ^a	IMC	0	M	Congenital herpes virus infection	Ca	FCA	-	-	Alive
P30 ^a	UCH	0	M	Necrotic enterocolitis	Ca	FCA	-	ITR	Alive
MD (n=8)									
		68	F	Malignancy	Cp	ITR	-	ITR	Dead
		76	M	Malignancy	Cp	FCA	-	-	Alive
		82	M	Malignancy	Ct	/	FCY	ITR	Dead
		58	F	Malignancy, DM	Ca	APH	-	-	Alive
		62	M	Malignancy, DM, thrombophlebitis	Ca	APH	-	-	Alive
		9	M	Malignancy	Cp	FCA/CAS/VOR	ITR	-	Alive
		65	M	Malignancy, ileus	Ca	FCA	-	-	Alive
		78	M	Malignancy	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 POS	-	Alive

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WILEY mycoses

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 Medic⁶ | Ivanka Savić⁷ | Snežana Delić⁸ | Suzana Nestorović Laban⁹ | Zorica Vasiljević¹⁰ | Mirjana Hadnadjev¹¹

Retke, preteće gljive u Srbiji (1)

What lurks in the sellar?

Sanda 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 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

decreased to 100 mU L⁻¹

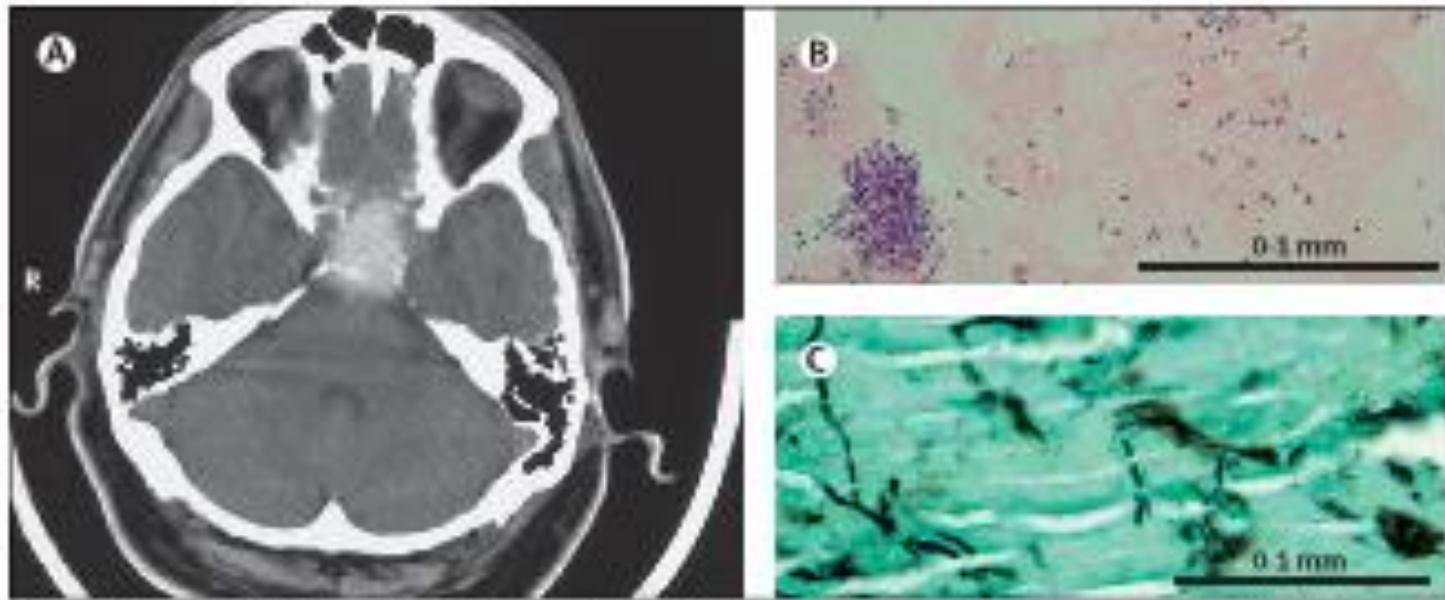
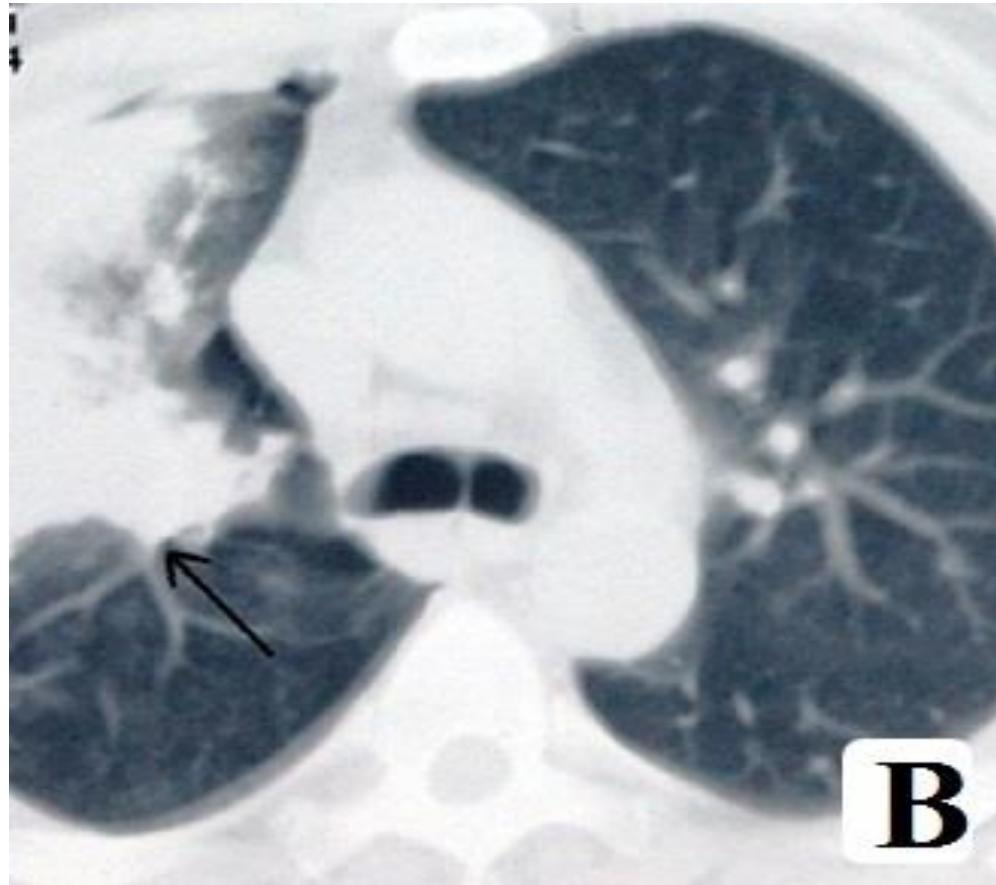


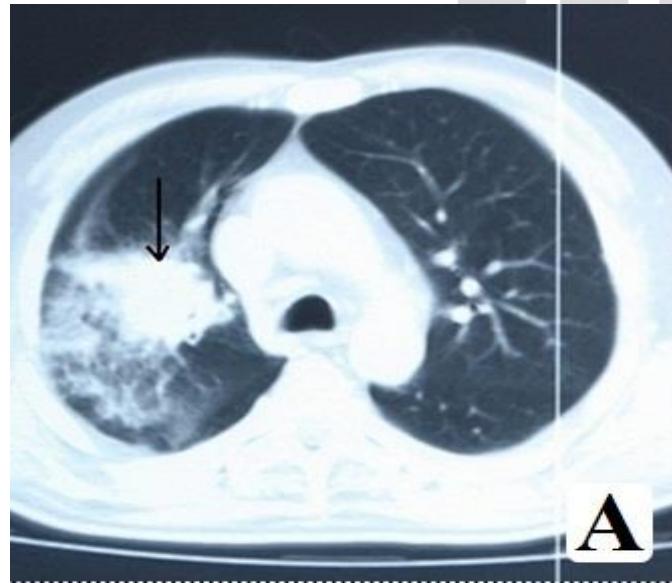
Figure: CT and histology of sellar contents obtained at surgery

(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 $\times 400$).

Retke, preteće gljive u Srbiji (2)



B

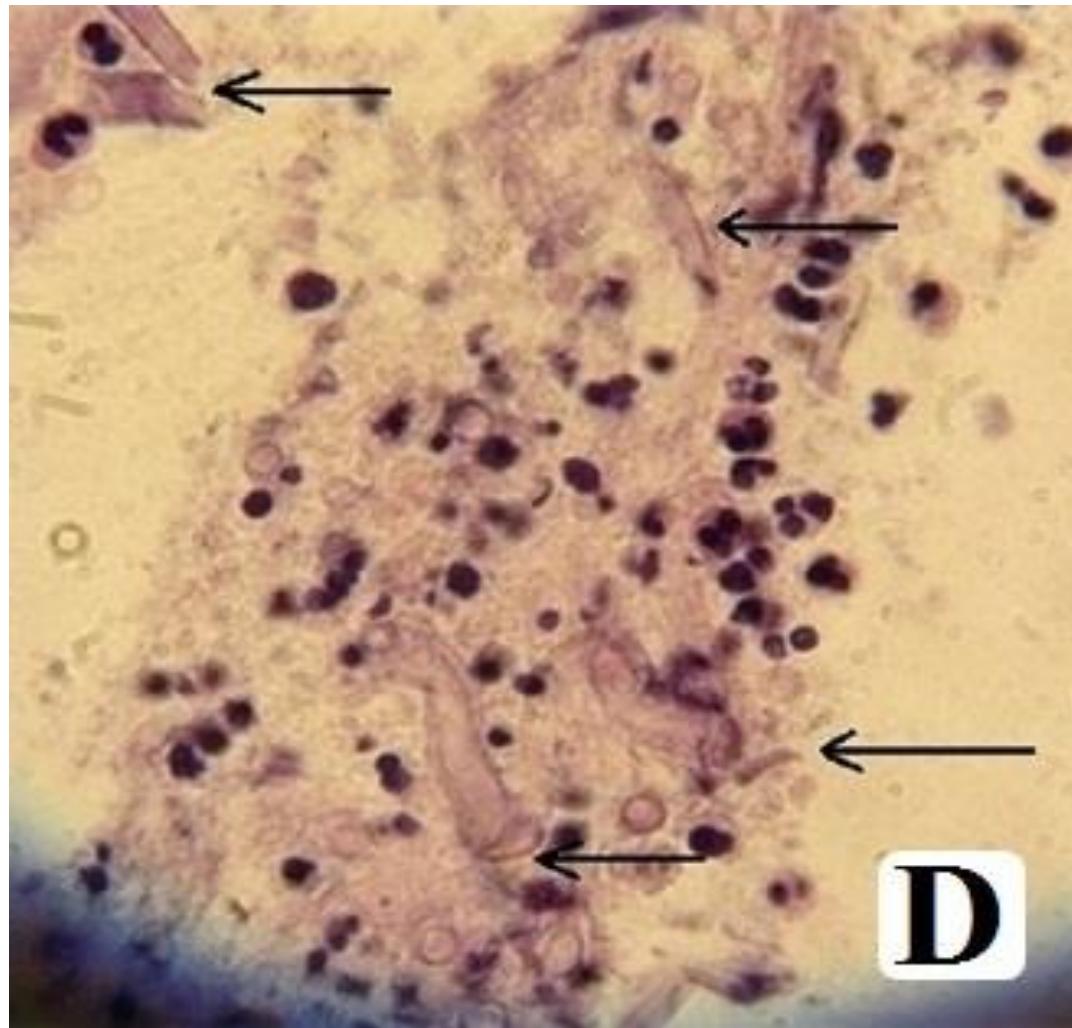


A



C

Retke, preteće gljive u Srbiji (2)



Retke, preteće gljive u Srbiji (3)



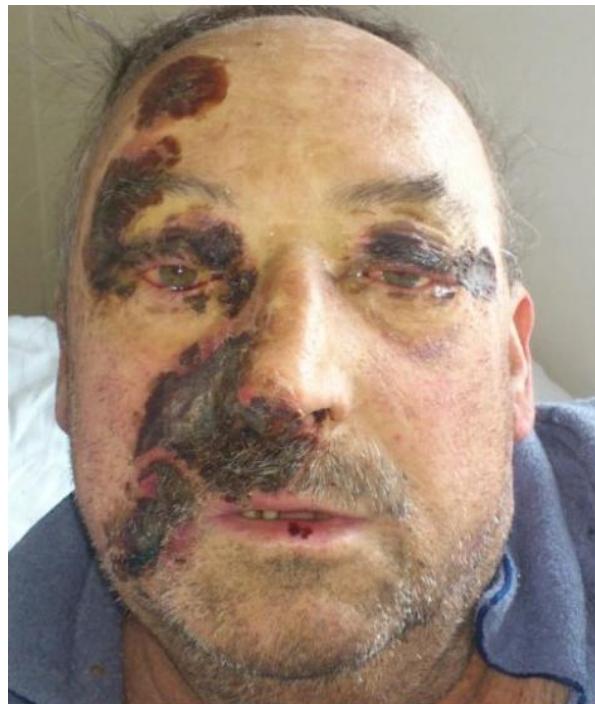
7. dan od početka Th Amfocil-om



14. dan od početka Th Amfocil-om



Amb terapija



5. dan od početka Th Amfocil-om

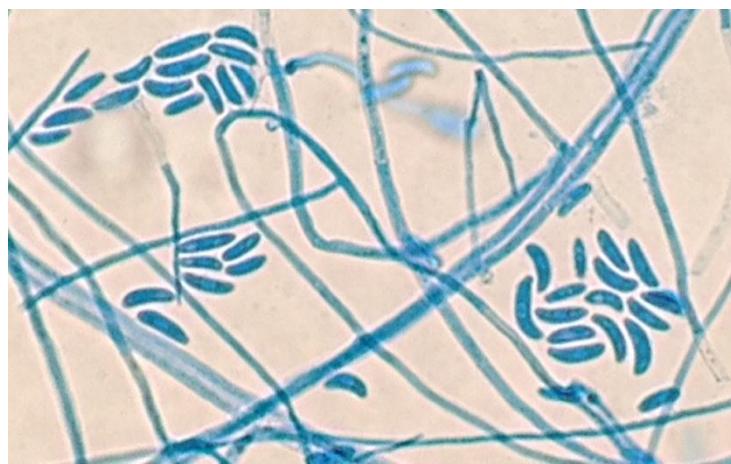
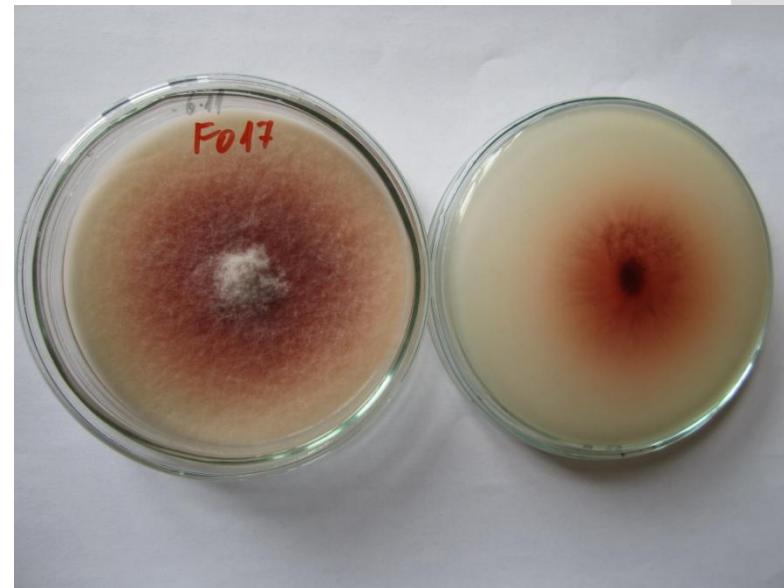
7. dan od početka Th Amfocil-om

14. dan od početka Th Amfocil-om





Hemokultura – hialine plesni



PLESNI

VRSTE	EPIDEMIOLOGIJA	FAKTORI RIZIKA	KLINIČKA SLIKA
<i>A. fumigatus</i>	Vodeći uzročnici letaliteta ("BMT"/leukemije)	"BMT" Neutropenija Transplantacija pluća Th steroidima HIV	Nespecifična Primarno pneumonia Primarno sinuzitis Diseminacija CNS
<i>A. flavus</i>	Inhalacija spora		
<i>A. niger</i>			
<i>A. terreus</i> *	Rezistencija na AM*		
<i>Mucor</i>	Porast incidencije	Hematoonkologija	Rino-orbito-cerbralna forma (50%),
<i>Rhisopus</i>	Inhalacija spora	Neutropenija	Kožna forma (16%),
<i>Rhisomucor</i>	Inokulacija spora/koža	Imunosupresija	Pulmonalna forma (10%)
<i>Absidia</i>	Ingestija spora	Diabetes mellitus	
<i>Scedosporium</i> (<i>P boydii</i>)	Kolonizacija kod CF Rezistencija na AM	Neutropenija Trauma/operacije Poplave	Visoka T ne reaguje na AB Promene na koži Diseminacija u CNS
<i>Fusarium</i>	Rasprostranjene gljive Lezije na kože	Neutropenija Trauma	Kožne promene (90%) Pluća i sinus (70%) HK (+)

K V A S N I C E

VRSTE

C. albicans
C. parapsilosis
C. glabrata
C. tropicalis
C. krusei

C. neoformans

C. gatii

Rhodotorula

Trichosporon

Malassezia

EPIDEMIOLOGIJA

Porast incidencije IK
Porast incidencije non-*albicans* vrsta
Porast rezistencije

Oporunisti
Primarno patogeni
Eucaliptus

“Emerging” infekcije
kod ID osoba

FAKTORI RIZIKA

CVK
Hemodializa
Neutropenija
Th steroidima/AB
Operacije
Kolonizacija

AIDS
T ćelijski deficit
Th steroidima

CVK
Parenteralna ishrana
Neutropenija
Th steroidima

KLINIČKA SLIKA

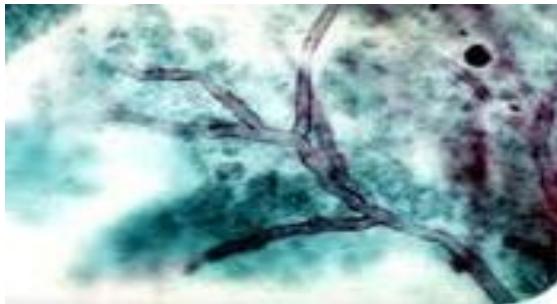
Nespecifična
Sepsa ne reaguje na AB

Meningoencefalitis
Pneumonija
Lezije na koži

Diseminove infekcije
/slične IK/

Dijagnostika retkih, pretećih gljive

Citologija



Kultura



BRZA, JEFTINA, DOKAZUJE SVE GLJIVE

Niska senzitivnost

Invazivne procedure uzorkovanja

Neophodan ekspert za detekciju gljiva

Neophodna strucna interpretacija nalaza

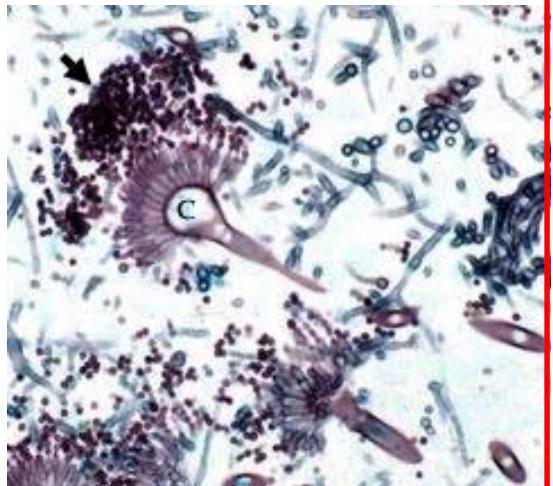
SPORA, JEFTINA, IZOLUJE VEĆINU GLJIVA

Spora metoda, niska senzitivnost,

Invazivne procedure uzorkovanja

DOKAZANE

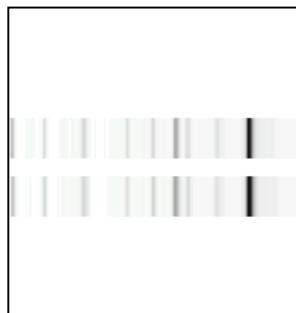
Neočekivane gljive
Identifikacija
Antimikogram



citologija



kultura



Identifikacija



Antimikogram
(S, I, R)

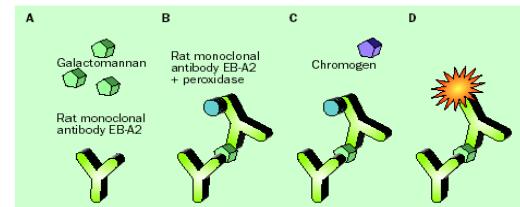


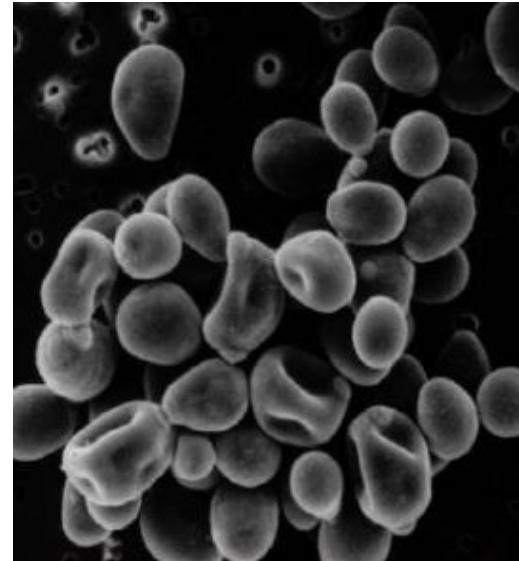
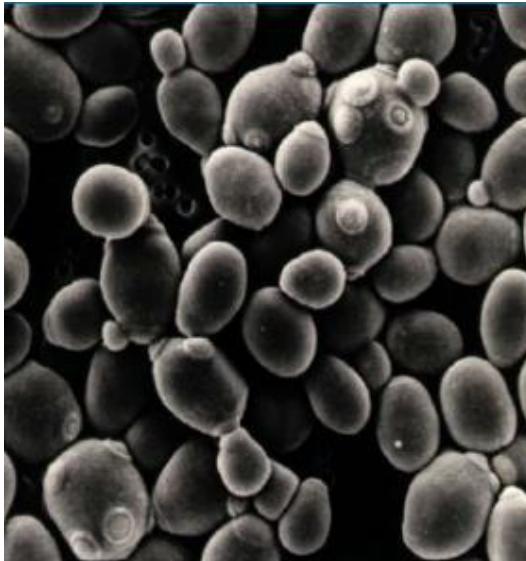
Figure 1. The Platelia Aspergillus ELISA technique. A serum ratio is calculated by dividing the optical density of the patient's serum sample by the mean optical density of two threshold control samples that contain 1 µg/L of galactomannan.

Biomarkeri

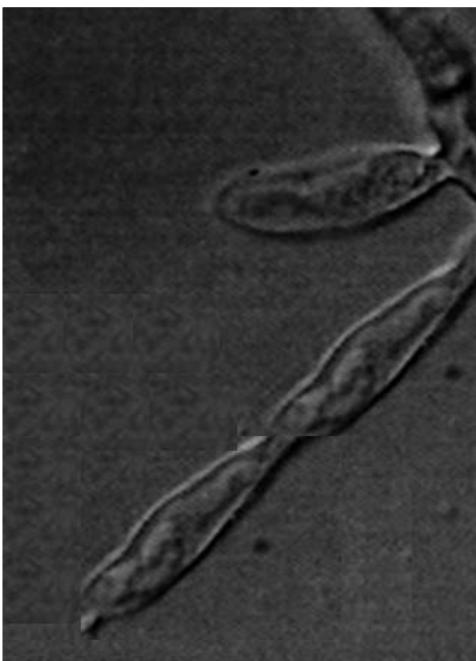
Fungistatski

Fungicidni

Candida



Aspergillus



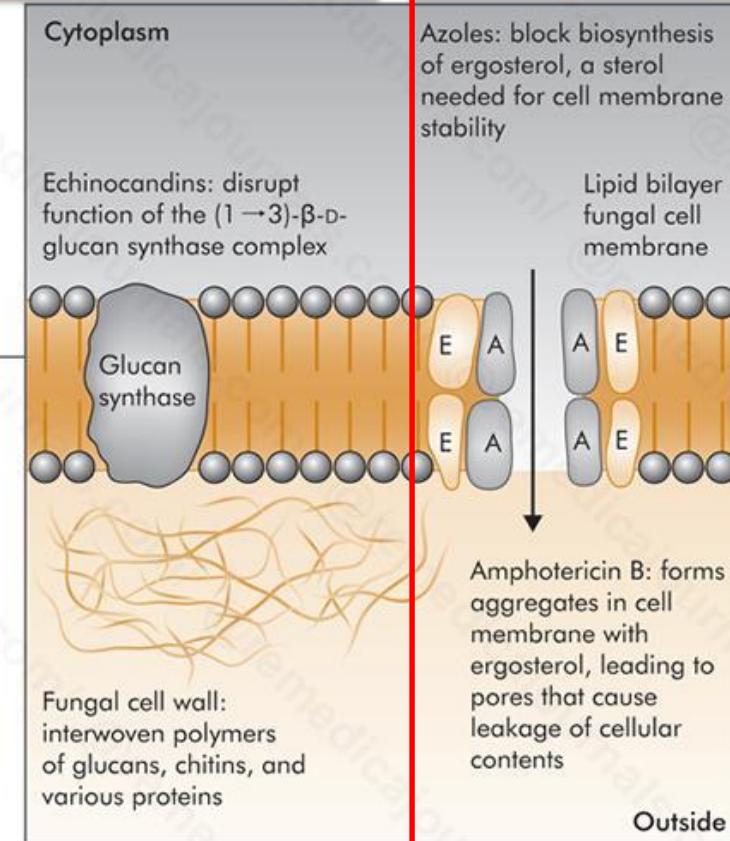
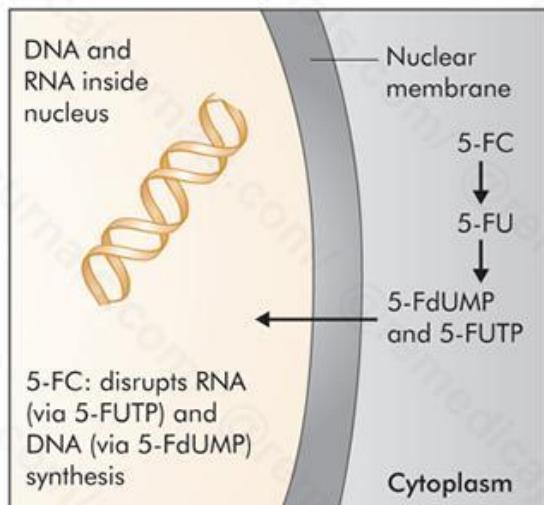
Terapija retkih, pretečih gljivičnih infekcija

Profilaktički

Empirijski

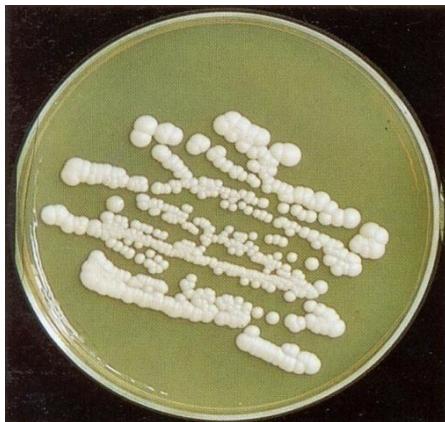
"Preemptive"

Specifični

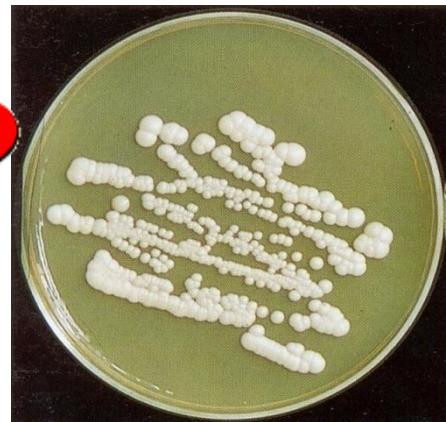


5-FC: 5-fluorocytosine; 5-FdUMP: 5-fluorodeoxyuridine monophosphate; 5-FU: 5-fluorouracil; 5-FUTP: 5-fluorouridine triphosphate; A: amphotericin B; E: ergosterol. Redrawn from [57], with permission from Elsevier.

Identifikacija i tipizacija gljiva

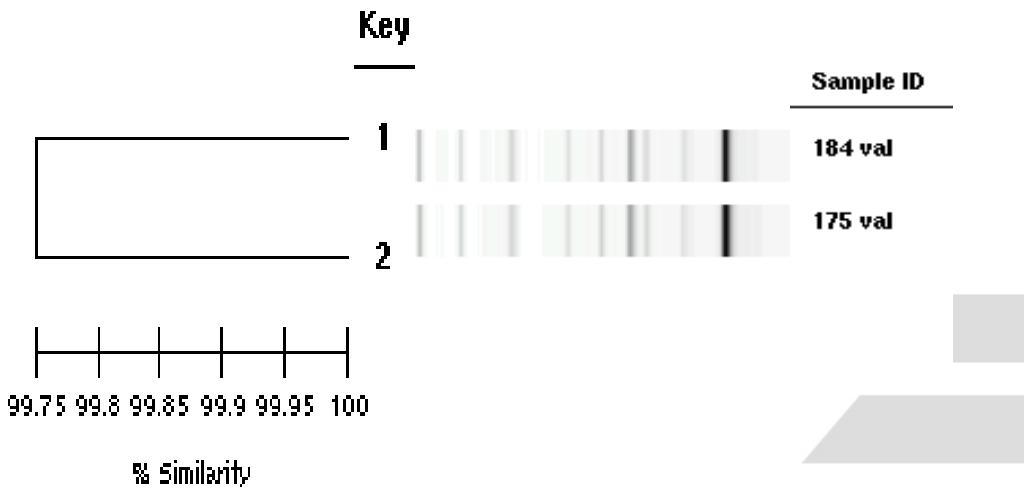


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Rep-PCR strain typing

Diversilab v3.3
PC
#40



Journal de Mycologie Médicale (2012) 22, 243–248



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ORIGINAL ARTICLE/ARTICLE ORIGINAL

In vitro antifungal activities of amphotericin B, 5-fluorocytosine, fluconazole and itraconazole against *Cryptococcus neoformans* isolated from cerebrospinal fluid and blood from patients in Serbia

Activité antifongique in vitro de l'amphotéricine B, de la 5-fluorocytosine, du fluconazole et de l'itraconazole sur des souches de Cryptococcus neoformans isolées du liquide cérébrospinal et du sang de patients en Serbie

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

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

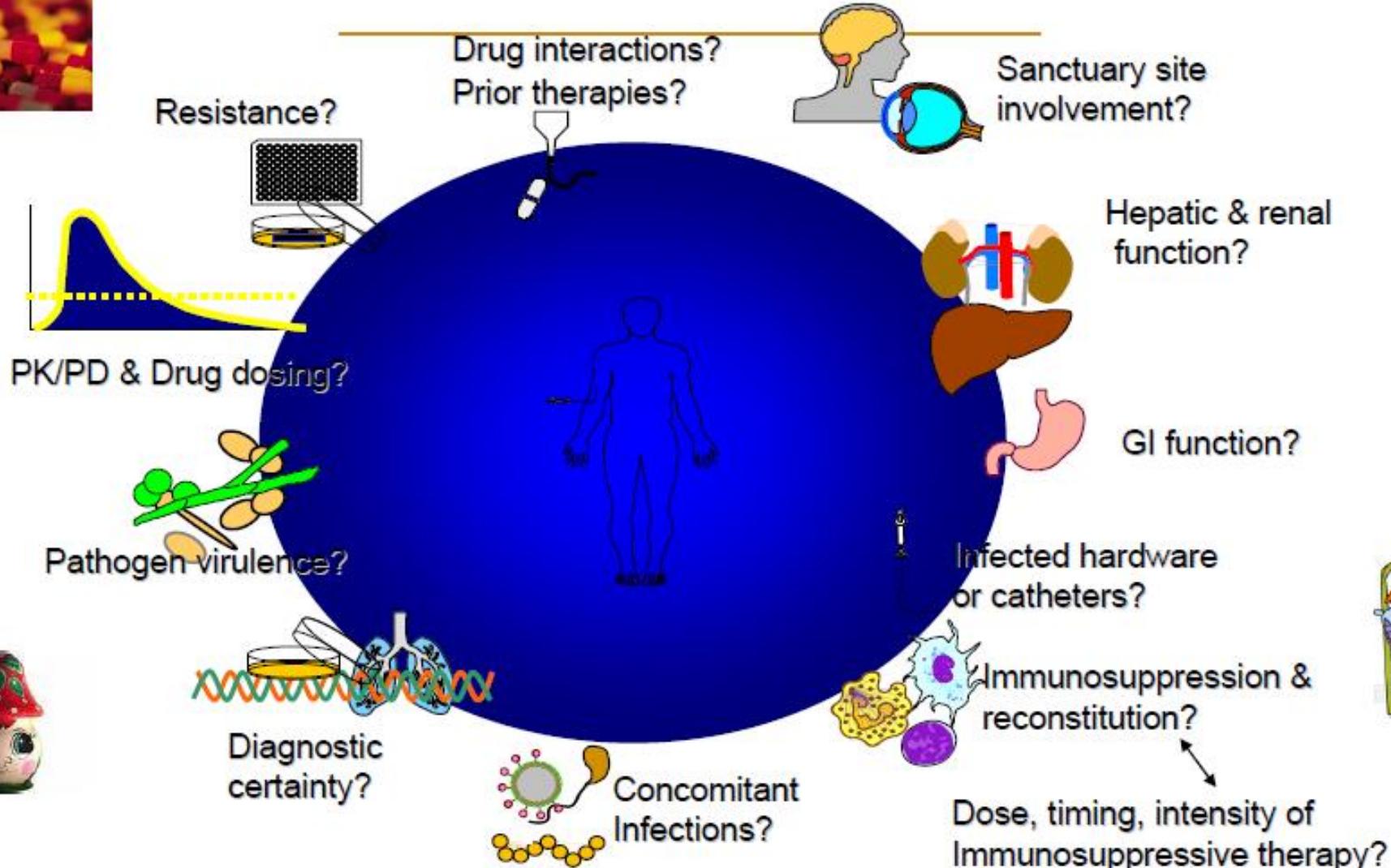
Pravovremena i tačna laboratorijska dijagnostika

Rare Moulds Guideline – u izradi



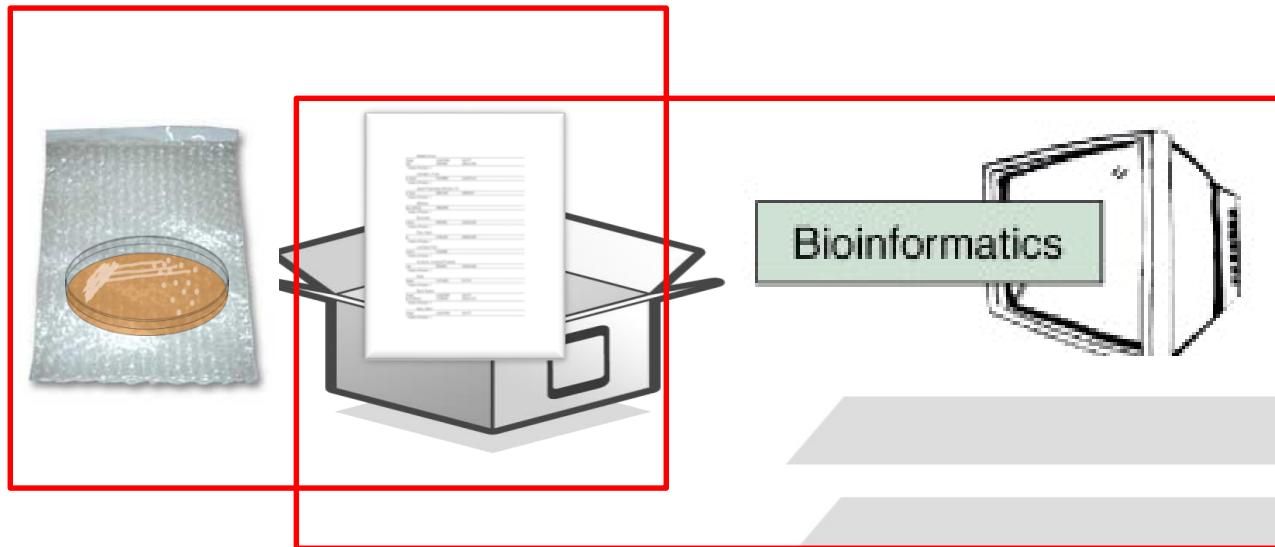
Društvo medicinskih
mikologa Srbije
Serbian Society of
Medical Mycology

Individualni pristup dijagnoze GI kod visokorizičnih pacijenata



Cilj – kreiranje testova za pravilno uzorkovanje i rano dokazivanje gljivica **MYCOPACK**

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



Self screening OR point of impact testing



Balkan Fungus 2018

First Balkan Conference
on Medical Mycology and Mycotoxicology



September 13-15, 2018
Timișoara - Romania

