ΠΜΣ Λοιμώξεις

Συστηματική Καντιντίαση
Καντινταιμία

Νικόλαος Β. Σύψας
Παθολόγος – Λοιμωξιολόγος
Ιατρική Σχολή ΕΚΠΑ
ΓΝΑ « Λαϊκό»

Η συστηματική καντιντίαση: είναι σημαντική για τον κλινικό;

Η συχνότητα της αυξάνει

Έχει μεγάλη νοσηρότητα και θνησιμότητα

Η επιδημιολογία της μεταβάλλεται

Non-albicans *Candida* spp.

Υπάρχει πρόβλημα αντοχής

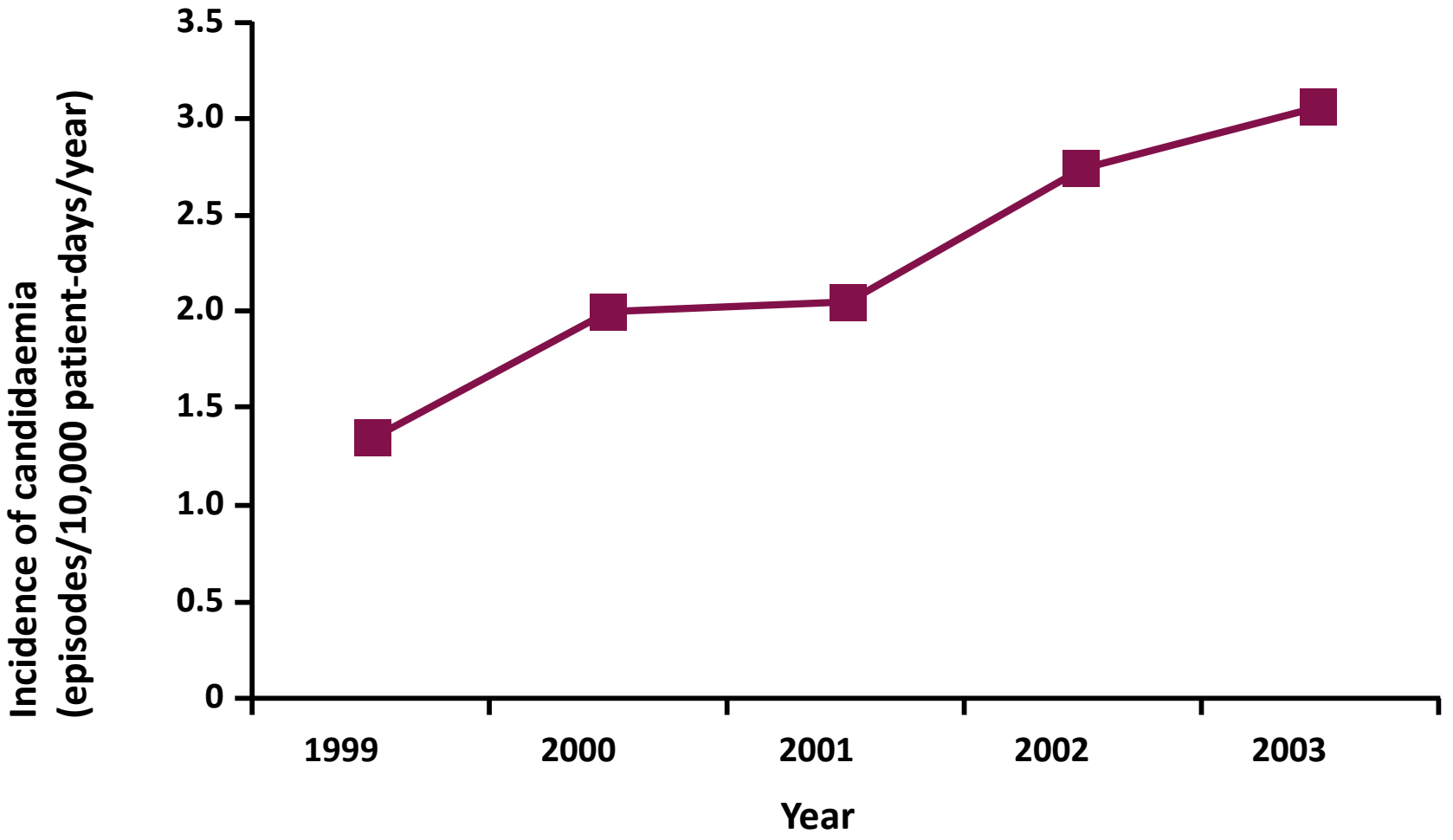
Νέα αντιμυκητιασικά φάρμακα μπαίνουν στην κλινική πράξη

Επιδημιολογία

Αυξανόμενη συχνότητα

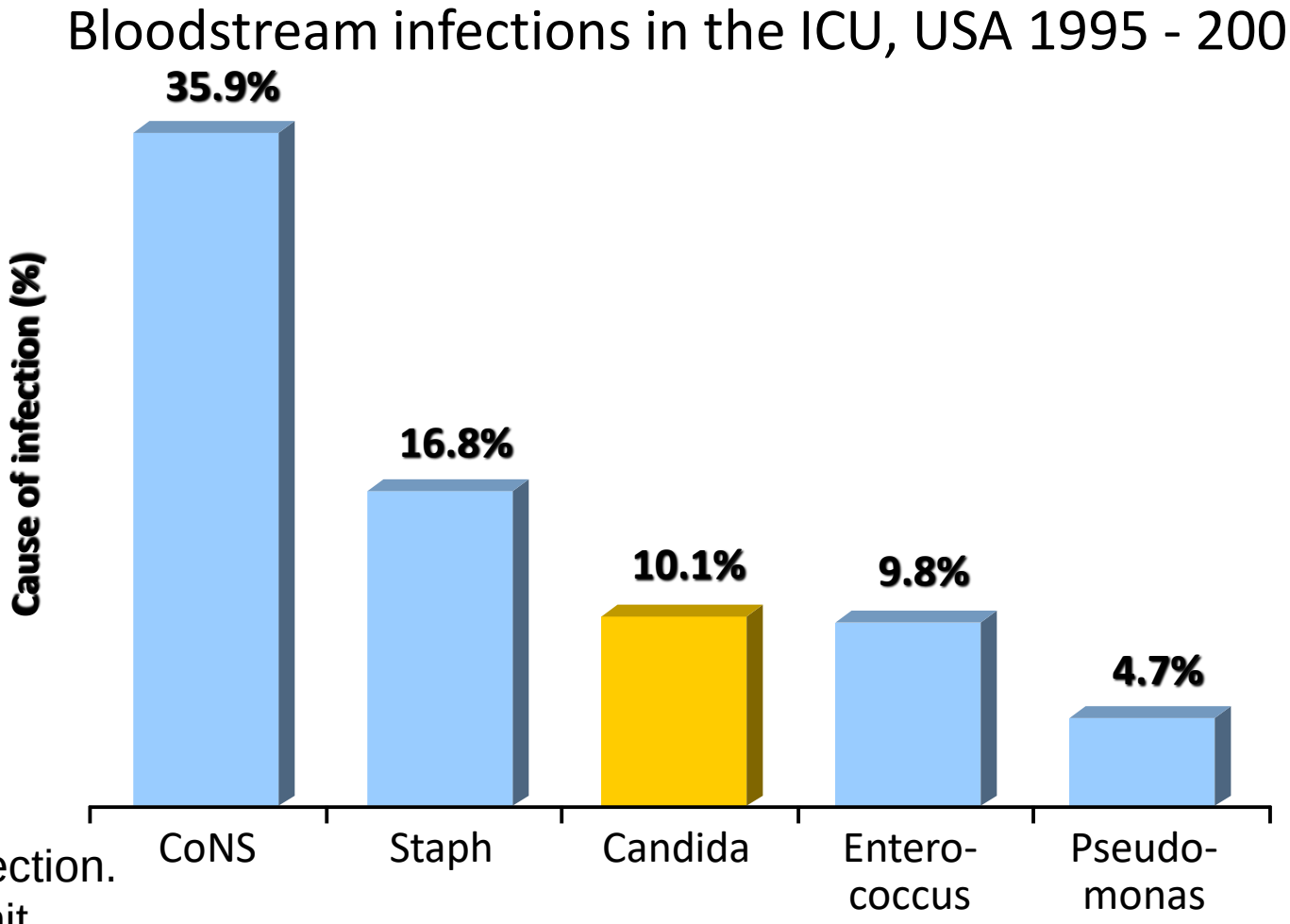
Μεγάλη θνησιμότητα

Αύξηση στη συχνότητα των συστηματικών λοιμώξεων από *Candida* στην Ευρώπη



Bassetti M, *et al*. *BMC Infect Dis* 2006; **6**:21

Candida is the 3rd most common cause of bloodstream infections in the ICU



BSI=Blood stream infection.
ICU=Intensive care unit.

Wisplinghoff H et al. Clin Infect Dis. 2004;39:309-317.

Επιδημιολογία

Αποτελούν το 12% των ενδονοσοκομειακών μικροβιαιμιών

Hidron AI, et al.: annual summary of data reported to the National Healthcare Safety Network at the Centers for Disease Control and Prevention, 2006–2007.
Infect Control Hosp Epidemiol 2008, 29:996–1011.

Στους ανοσοκατασταλμένους ασθενείς η επίπτωση είναι μεγαλύτερη έως 28%

Kontoyiannis DP et al. Prospective surveillance for invasive fungal infections in hematopoietic stem cell transplant recipients, 2001-2006: overview of the Transplant-Associated Infection Surveillance Network (TRANSNET) Database.
Clin Infect Dis. 2010 ;50:1091-100

Η κορυφή του παγόβουνου;

Νεκροτομική μελέτη σε 720 ασθενείς με αιματολογικές κακοήθειες

94 είχαν συστηματική καντιντίαση την στιγμή του θανάτου

Μόνο 24 είχαν θετική καλλιέργεια αίματος πριν καταλήξουν . Προφύλαξη;

Kami M, et al. Effect of fluconazole prophylaxis on fungal blood cultures: an autopsy-based study involving 720 patients with haematological malignancy. Br J Haematol. 2002;117:40

Θνησιμότητα

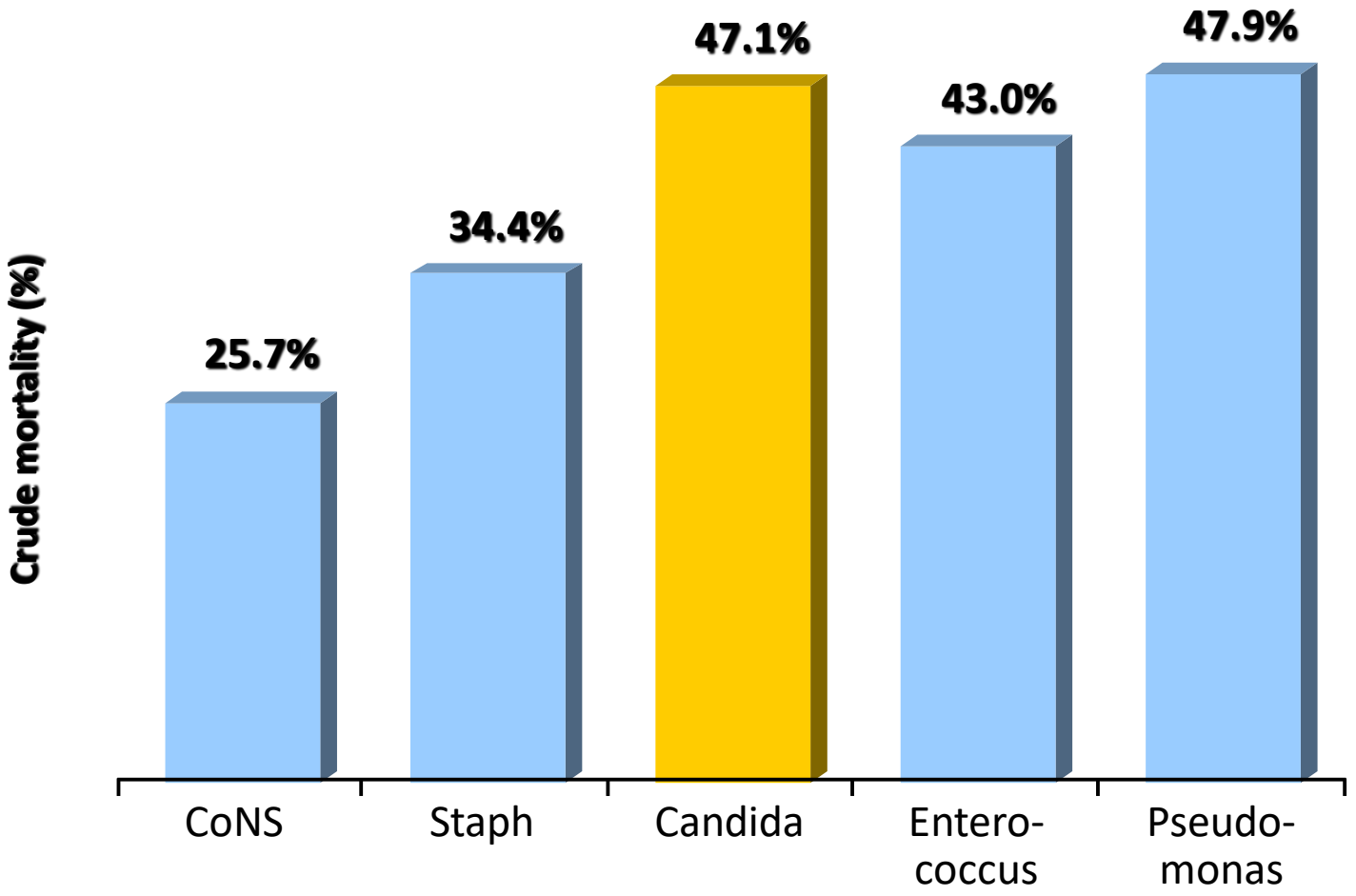
Parameter	No. of episodes	Mortality (%)	*p* value
Aetiological agent			
C. albicans	1,090	38.5	0.65
C. glabrata	269	45.0	0.02
C. parapsilosis	263	25.9	< 0.001
C. tropicalis	140	41.4	0.42
Underlying condition			
Surgery	892	35.3	0.26
Intensive care	791	42.4	0.02
Solid tumour	442	49.2	< 0.001
Haematological malignancy	247	44.9	0.03
HIV infection	61	23.4	0.03
Premature birth	123	26.8	0.02
Age group			
< 1 year	142	26.0	0.006
1 19 years	148	22.3	< 0.001
20 69 years	1,096	36.6	0.46
	556	47.7	< 0.001
Total population	1,942	37.9	

Tortorano AM, *et al*. *Eur J Clin Microbiol Infect Dis* 2004

IC is associated with high mortality in the ICU

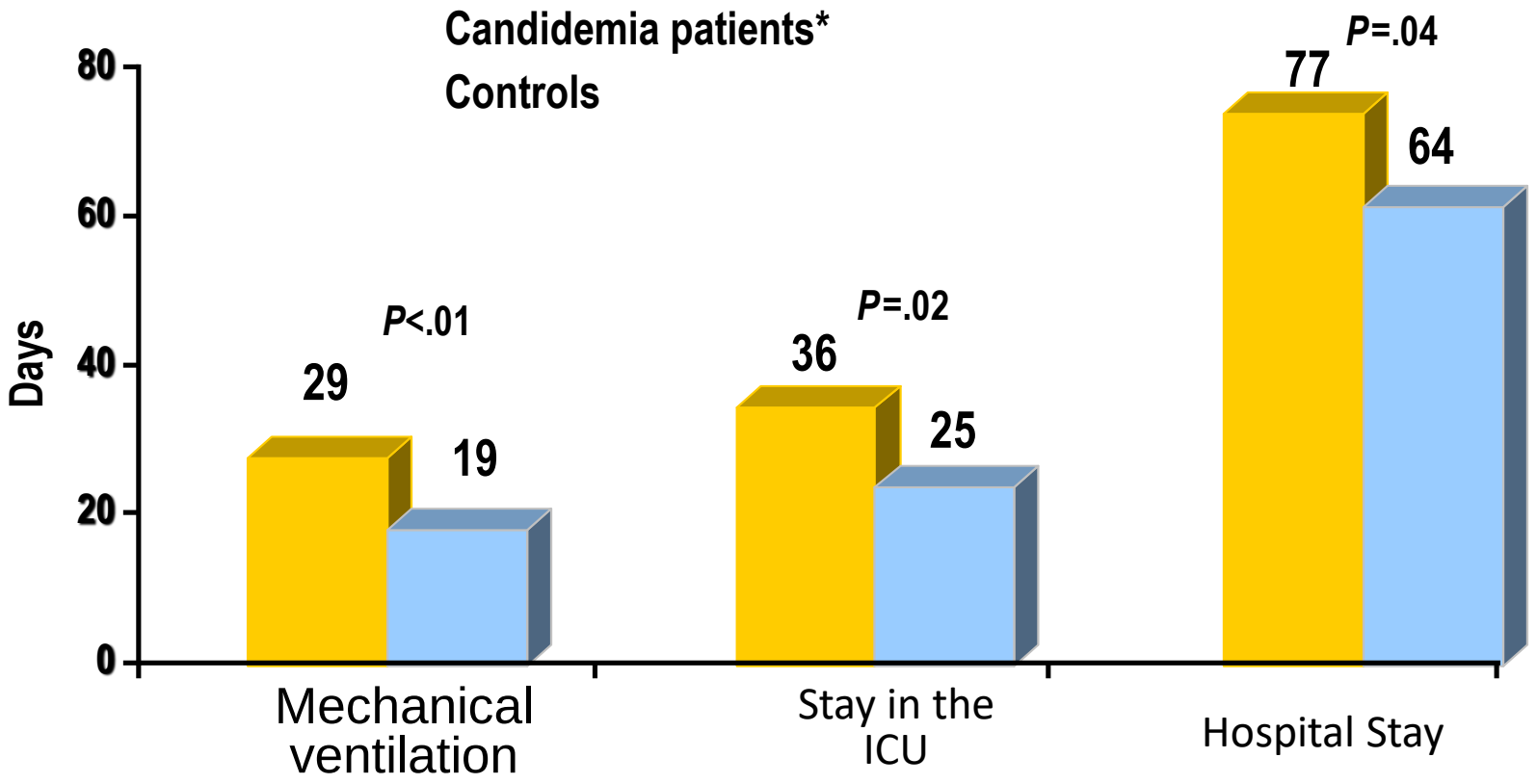
Crude mortality

Five most common bloodstream pathogens in the ICU, 24,179 cases, U.S., 1995-2002



Wisplinghoff H et al. *Clin Infect Dis*. 2004;39:309-317.

IC prolongs ICU and hospital stay



Blot SL et al. *Am J Med*. 2002;113:480-485

IC increases costs

	Candidemia (n= 8,949)	No candidemia (n= 17, 267)	Increase (95% CI)
Mortality	30.6	16.1	14.5 (12.1-16.9)
Length of stay	18.6	8.5	10.1 (8.9-11.3)
Cost (US $ per patient)	66,154	26,823	39,331 (33,600-45,602)

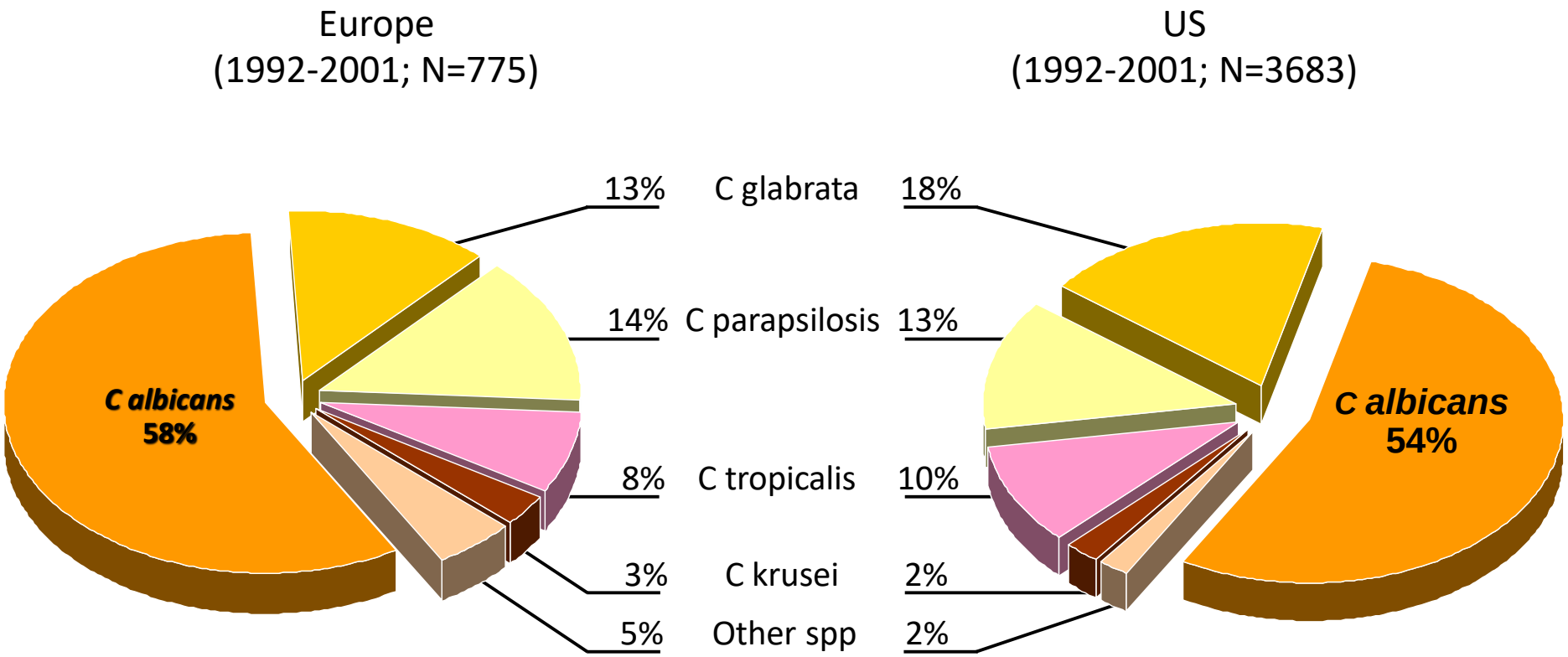
Source Adults: Nationwide Inpatient Sample 2000;

Clin Infec Dis 2005; 41:1232-9

Η επιδημιολογία μεταβάλλεται

Non-albicans Candida spp.

Κατανομή των *Candida* species το 2004

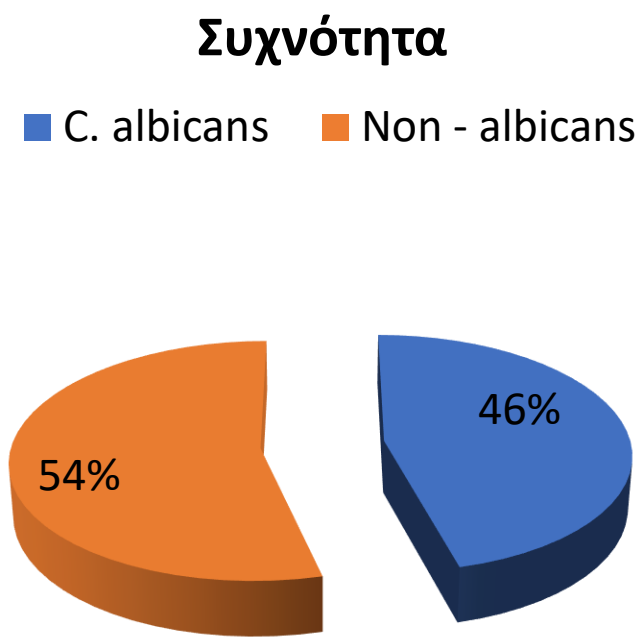


Pfaller MA et al. Clin Microbiol Infect. 2004;10(suppl 1):11-23.

Κατανομή των *Candida* species 2009

Prospective Antifungal Therapy (PATH) Alliance database

2019 ασθενείς καταγράφηκαν , μεταξύ 1 -7-2004 και 5- 3-2008



Horn DL, et al. Epidemiology and outcomes of candidemia in 2019 patients: data from the prospective antifungal therapy alliance registry. Clin Infect Dis. 2009;48:1695-703.

Ελληνική εμπειρία

Αιματολογικοί ασθενείς

Ελληνική εμπειρία 2009-2011

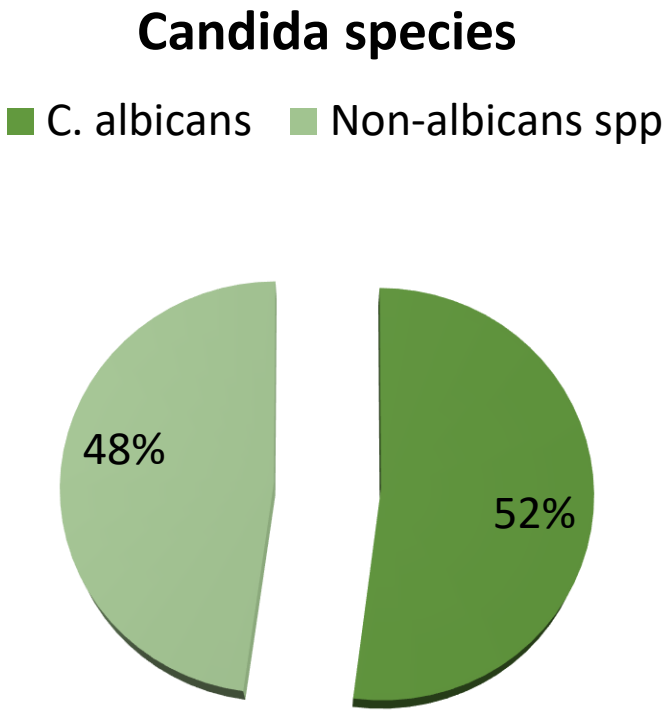
Προοπτική

Πολυκεντρική (n=9)

1,158,018 μη-αιματολογικοί ασθενείς

N=967 επεισόδια καντινταιμίας

0.83 cases per 1,000 admissions



Gamaletsou M, et al. Clin Microb Infect 2014; 20: O50–O57

Επίπτωση της καντινταιμίας

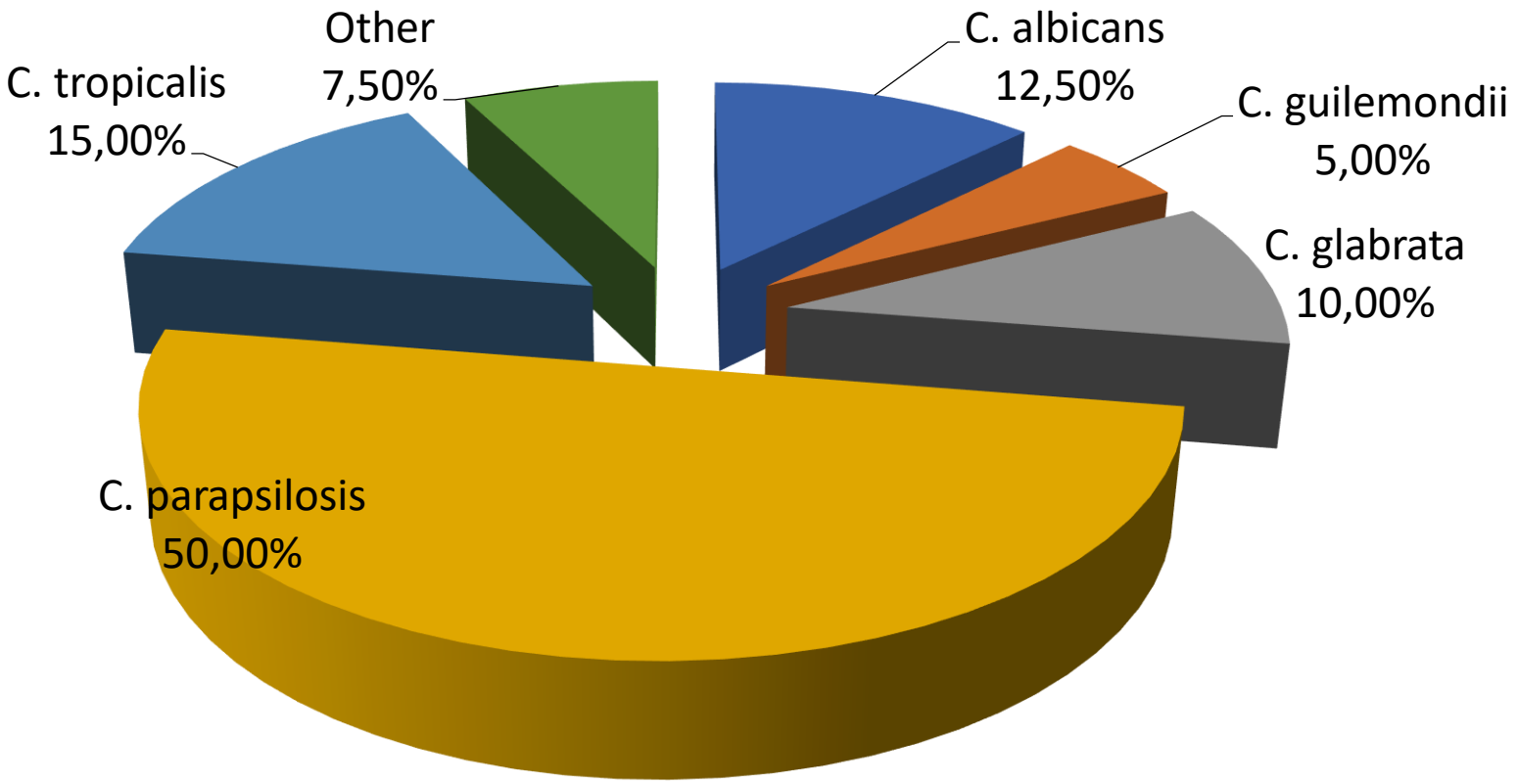
40 επεισόδια καντινταιμίας επί 27.864 εισαγωγών αιματολογικών ασθενών,

επίπτωση 1.4 /1000 εισαγωγές, 95% C.I.: (0.88, 1.98)

P<0.001

Gamaletsou M, et al. Clin Microb Infect 2014; 20: O50–O57

-2011



Gamaletsou M, et al. Clin Microb Infect 2014; 20: O50–O57

Ελληνική εμπειρία σε αιματολογικούς ασθενείς 2009-2011

Case control nested analysis: 80 controls

Risk-factors

- Central venous catheters,
- Hypogammaglobulinemia,
- High APACHE II score

Gamaletsou M, et al. Clin Microb Infect 2014; 20: O50–O57

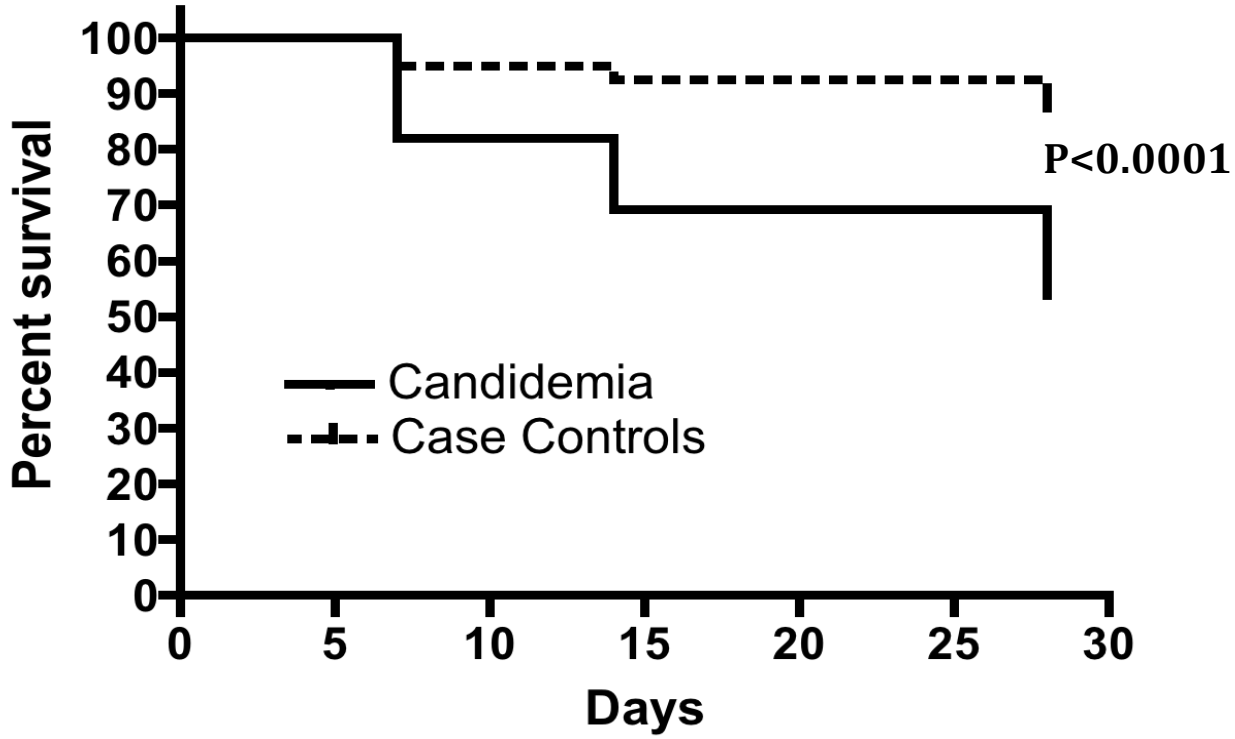
Ελληνική εμπειρία σε αιματολογικούς ασθενείς 2009-2011

Crude mortality at day 28:

- Hematology 18/40 (45%)
- Non-hematology 9/80 (11%)

Gamaletsou M, et al. Clin Microb Infect 2014; 20: O50–O57

Ελληνική εμπειρία σε αιματολογικούς ασθενείς 2009-2011



Gamaletsou M, et al. Clin Microb Infect 2014; 20: O50–O57

Γιατί αυξάνονται οι non-albicans?

Variable	Crude OR (95% CI)	*P*	Adjusted OR (95% CI)	*P*
Age by decade	1.20 (0.97–1.47)	.09	…	
Lung disease	1.54 (0.75–3.15)	.23	…	
Gastrointestinal procedure	1.33 (0.92–0.91)	.13	…	
Mean no. of antibiotics per day	2.02 (0.78–5.25)	.15	2.31 (0.71–7.54)	.17
Mean no. of platelet transfusions per day	2.11 (0.66–6.73)	.21	…	
No. of days of CVC use/no. of days at risk	1.43 (0.86– 2.36)	.17	1.95 (1.10–3.47)	.02
Proportion of days of fluconazole exposure	8.14 (1.87–35.4)	.01	11.6 (2.28–58.8)	.003
No. of days of TPN/no. of days at risk	0.50 (0.22–1.11)	.02	0.16 (0.05–0.47)	.009
No. of days of corticosteroid therapy/no. of days at risk	0.70 (0.37–1.35)	.29	…	

NOTE. CVC, central venous catheter; TPN, total parenteral nutrition.

Chow JK et al. Factors Associated with Candidemia Caused by Non-*albicans Candida Species* Versus *Candida albicans in the Intensive Care Unit.*

Clinical Infectious Diseases 2008; 46:1206–13

Non-albicans *Candida* spp are resistant to fluconazole (SENTRY study 2006-07)

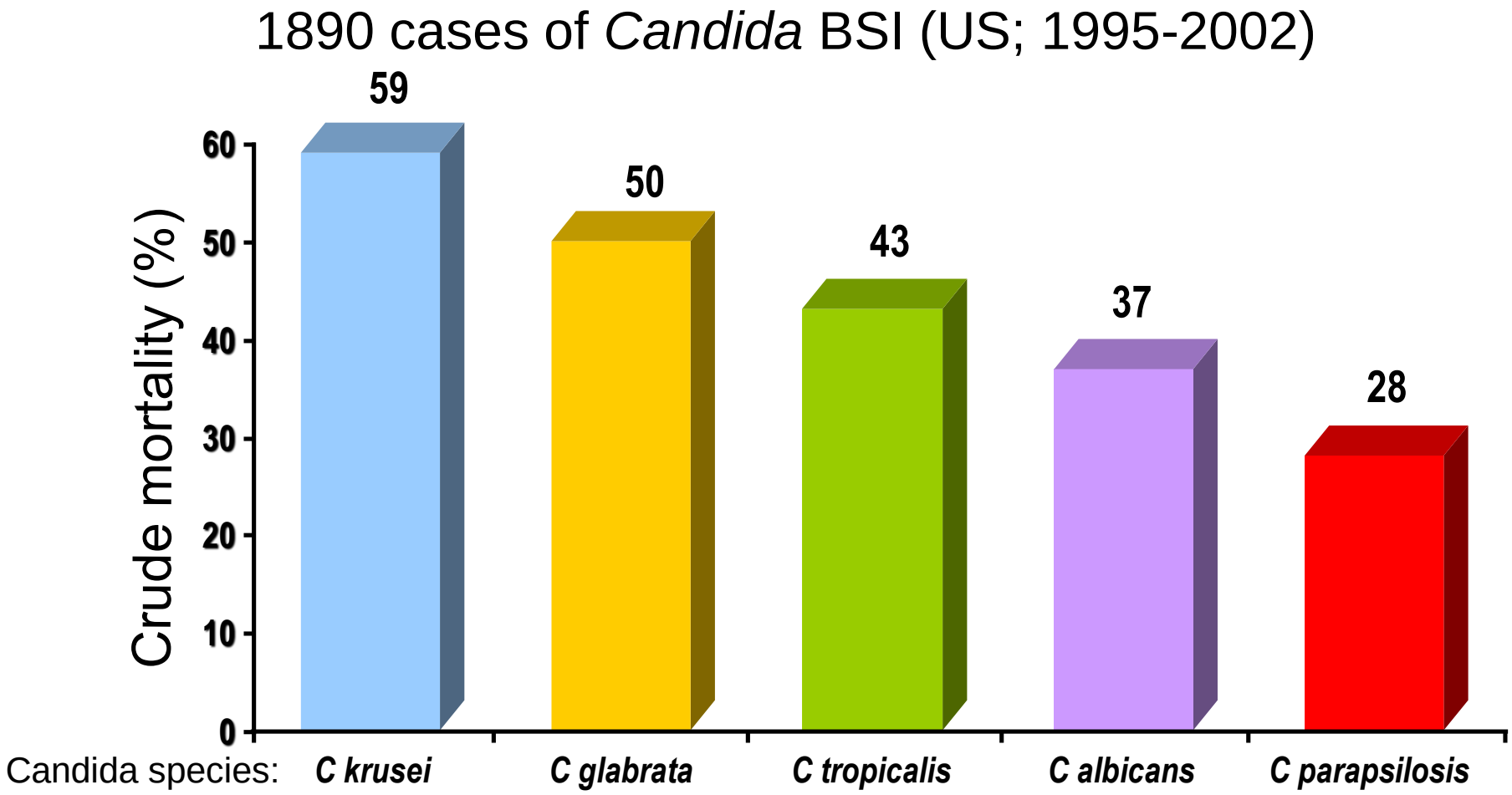
Species	Fluconazole MIC (µg/ml)			Percentage of isolates		
	50%	90%	Range	Susceptible	Susceptible–dose-dependent*	Resistant
Candida spp.	≤ 0.5	8	≤ 0.5 – >64	93.4	4.7	1.9
C. albicans	≤ 0.5	≤ 0.5	≤ 0.5–16	99.7	0.3	0
C. glabrata	8	64	≤ 0.5 – >64	74.3	15.3	10.4
C. parapsilosis	1	4	≤ 0.5–32	96.6	3.4	0.0
C. tropicalis	≤ 0.5	1	≤ 0.5–32	99.4	0.6	0.0
C. krusei	32	64	8 – >64	3.5	79.3	17.2

Messer SA, *et al*. *J Clin Microbiol* 2006; **44:**1782–1787.

Τα non-albicans στελέχη

Μεγαλύτερη αντοχή  μεγαλύτερη θνησιμότητα

Non-albicans *Candida* spp are associated with higher mortality

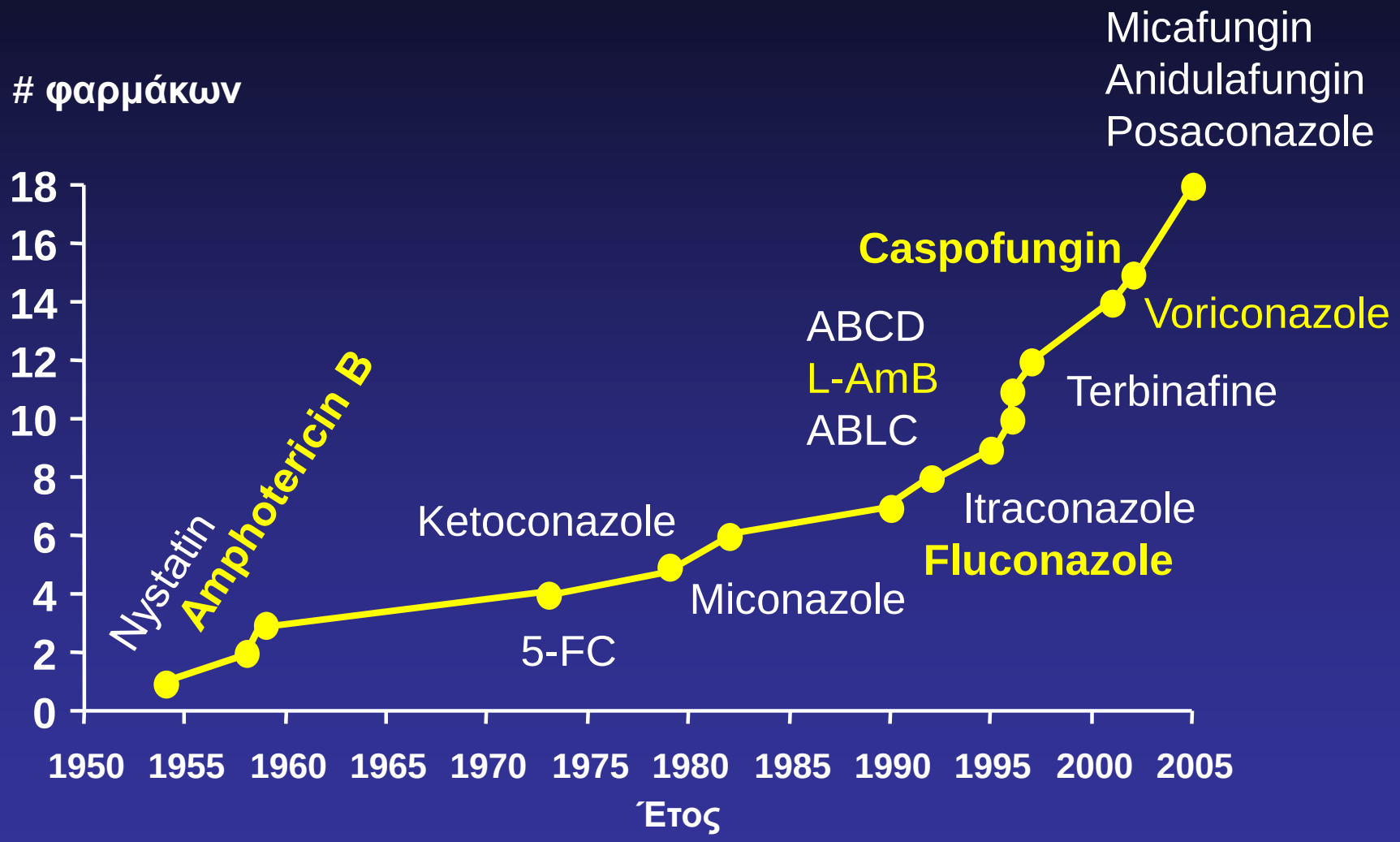


Adapted from Wisplinghoff H et al. Clin Infect Dis. 2004;39:309-317.

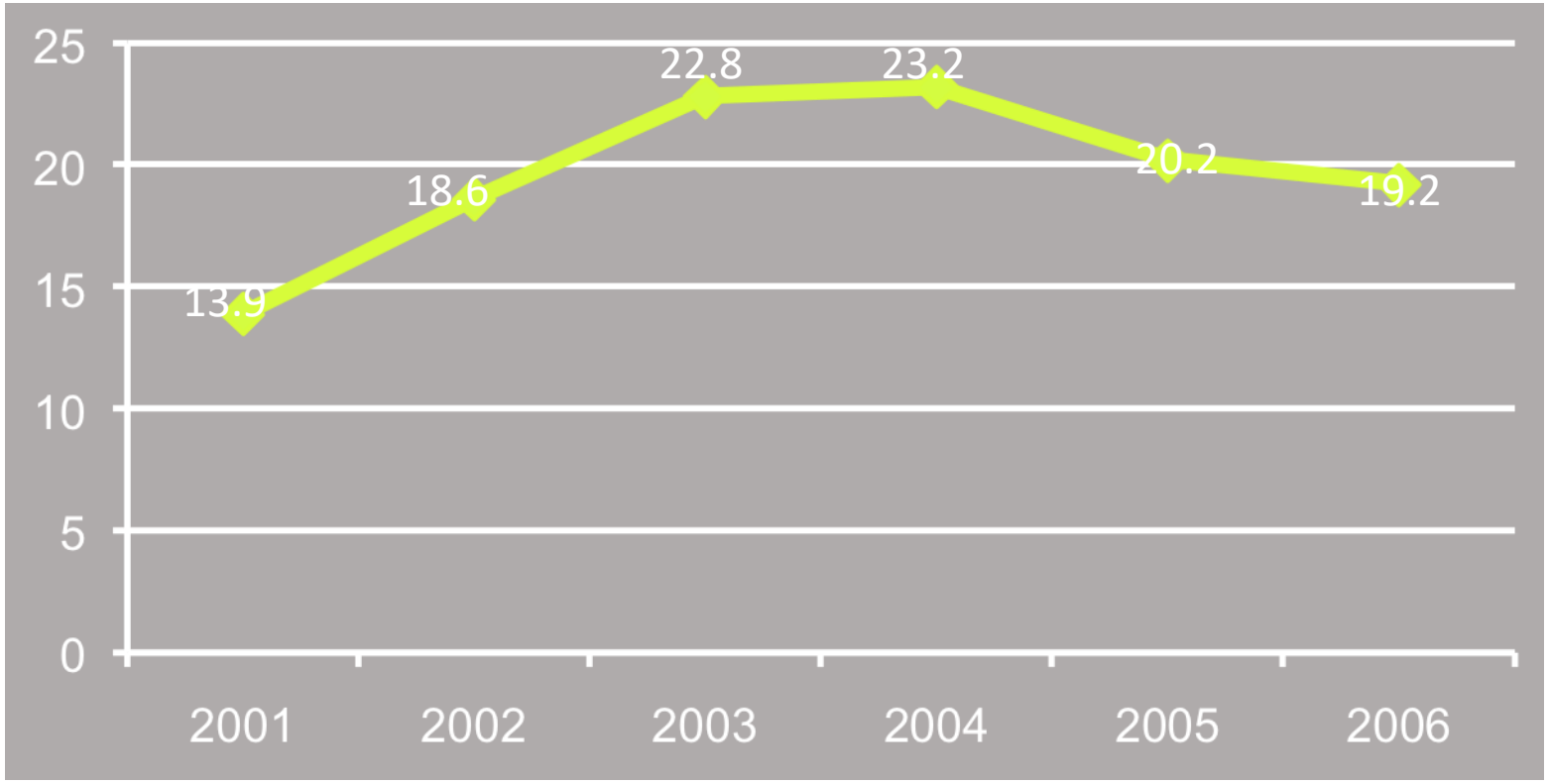
Νεώτερα αντιμυκητιασικά

Τι επίδραση είχε η εισαγωγή τους στην κλινική πράξη;

Επιτάχυνση στην ανακάλυψη νέων φαρμάκων



Επίπτωση της καντινταιμίας στο MDACC 2001-2007



Sipsas NV, et al.: Cancer 2009, 115:4745-4752.

p : NS

Θνησιμότητα

Στοιχεία που πάρθηκαν από 7 τυχαιοποιημένες κλινικές μελέτες θεραπείας της ΣΚ με νεώτερα φάρμακα έδειξαν ότι η συνολική θνησιμότητα μεταξύ των 1831 ασθενών την 30 ημέρα ήταν 31.9%.

Andes DR, et al.: Impact of therapy on mortality across candida spp in patients with invasive candidiasis from randomized clinical trials: a patient level analysis [abstract M-1312]. Presented at the 50th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), Boston, USA; September 12-15, 2010

Επιδημιολογία στο MDACC

	No. of patients (%)		
***Candida* species**	**1988–1992** **n=230**	**1993–2002** **n=281**	**2001-2007** **n=173**
C. albicans	79 (34)	38 (13)	41 (24)
Non-*albicans* species	139 (60)	227 (81)	129 (75)
C. glabrata	28 (12)	86 (31)	8 (5)
C. krusei	17 (7)	68 (24)	30 (17)
C. parapsilosis	33 (14)	39 (14)	42 (24)
C. tropicalis	53 (23)	27 (10)	37 (21)

Sipsas NV et al. Cancer 2009

Η εισαγωγή των νεώτερων αντιμυκητιασικών σε ασθενείς με αιματολογικές κακοήθειες

Συχνότητα της νόσου ?

Θνησιμότητα ?

Μετέβαλλαν την επιδημιολογία

Sipsas NV et al. Cancer 2009

Παθοφυσιολογία

Ομάδες / παράγοντες κινδύνου

Ένας θαρραλέος γερμανός ειδικευόμενος χειρουργικής!

Μέχρι το 1960's → η *Candida είναι πολύ μεγάλη για να περάσει από το έντερο στο αίμα*

Ένας ειδικευόμενος έκανε την υπόθεση ότι τα αντιβιοτικά → υπερανάπτυξη *Candida* στο έντερο→ μετακίνηση στο αίμα

Ανέθεσε σε 2 συναδέλφους του να τον παρακολουθούν και κατάπιε καλλιέργημα 10^{12} *C. albicans*

Candida translocation (persorption) after ingestion of a massive oral inoculum

FUNGÆMIA AND FUNGURIA AFTER ORAL ADMINISTRATION OF CANDIDA ALBICANS

W. KRAUSE
H. MATHEIS K. WULF
FROM THE LANDESKLINIK AND THE STADT-KRANKENHAUS, KASSEL, WEST GERMANY

Summary We have administered approximately 10^{12} cells of *Candida albicans* orally to a healthy volunteer. *C. albicans* cells were cultured from blood-samples taken after 3 and 6 hours, and from urine samples taken after $2^3/_4$ and $3^1/_4$ hours, and were found to be identical to the strain administered. There was a transient toxic reaction 2 hours after ingestion, and symptoms of fungæmia were observed up to 9 hours after the start of the test. No lasting damage resulted from the experiment. We conclude that *C. albicans* cells are capable of passing through the intestinal wall, probably by the mechanism of " persorption " and so reach the blood and urine. Since the population of *C. albicans* in the intestine was comparable to that sometimes seen after the use of broad-spectrum antibiotics, it seems likely that antibiotic-induced fungal overpopulation may also result in fungæmia.

Introduction

ANIMAL studies have shown that particles 5–10 μ in diameter can be absorbed intact from the intestinal tract, reach the bloodstream via the thoracic duct, and be detected in the urine. This was first described by Herbst in 1844, and was later confirmed by Hirsch (1906) and Verzar (1911). More recently the absorption were taken at the same times.

Laboratory values for blood and urine a week before the experiment were normal. The volunteer had for many months been on the normal hospital diet. From 24 hours before the test, he took no food and drank only unsweetened black tea. At the start of the test, rectal temperature was 37·1°C, blood-pressure 145/100 mm. Hg, and heart-rate 88 per minute.

Administration of Candida

C. albicans, strain No. 70310 (Hamburg), was used. A week before, and on the day of the experiment, the strain was investigated for purity by the method of Lodder and Kreger-van Rij (1968) in the mycological laboratory of the Municipal Hospital, Kassel. A total of 80 g. of *C. albicans* was grown in the same laboratory using Sabouraud-dextrose-agar without inhibiting (antibiotic, chemotherapeutic) or growth-stimulating substances (such as vitamins).

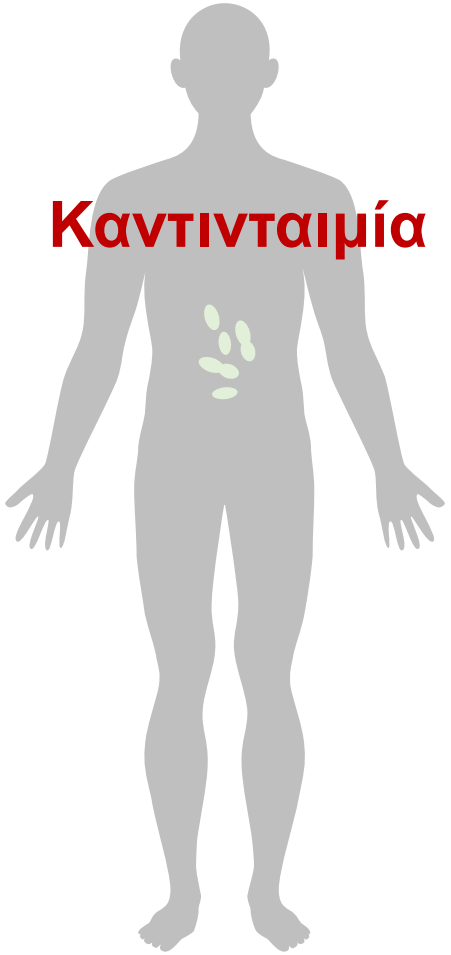
As 200 mg. of *C. albicans* was expected to grow on each culture-medium plate, 400 plates were inoculated. The cultures were investigated for bacterial and fungal contamination. From them 80 g. of *Candida* cells (free from culture-medium particles) was taken and a suspension was made in 100 g. of physiological saline solution, producing a liquid-pulpy suspension of 180 g. which contained at least 10^{12} *C. albicans* cells. The suspension was prepared half an hour before administration. Shortly before the volunteer swallowed it, the suspension was again sampled for control cultures and slides.

10 minutes after taking the suspension, the volunteer drank 200 ml. of non-carbonated mineral water to wash down the residues and an hour later he drank 400 ml. of physiological saline solution. As the reaction to the massive dose of living pathogenic fungi could not be predicted, all measures for emergency treatment were ready.

After 2 hours the subject felt very ill; at 3, 7, and 9 hours, rectal temperature was 38·7°C; he was shivering and had a severe headache. These signs and symptoms appeared to indicate a toxic reaction and fungæmia. $3^1/_2$

Krause et al. *Lancet* 1969;1:598-599.

Ιατρική παρέμβαση		Ρόλος στη λοίμωξη
Αντιβιοτικά (αριθμός - διάρκεια)	→	Αποικισμός από μύκητες
Κεντρικοί καθετήρες	→	Άμεση IV πρόσβαση
Ολική παρεντερική διατροφή	→	Άμεση IV πρόσβαση Μολυσμένο περιεχόμενο
Μεγάλα χειρουργεία (κυρίως ΓΕΣ)	→	Βακτηριακή μετακίνηση στην κυκλοφορία
Χημειοθεραπεία (ουδετεροπενία)	→	Ανοσοκαταστολή/ βλεννογονίτιδα
Κορτικοστεροειδή	→	Ανοσοκαταστολή
Μεγάλη ηλικία	→	Ανοσοκαταστολή, Συν-νοσηρότητες



Gamaletsou MN *et al. Curr Fung Infect Reports* 2011; 5: 34-41.

Κλινική εικόνα

Clinical spectrum of IC

Candidemia: Non-specific symptoms and signs similar to that of bacteremia

- From: Protracted fever not responding to broad-spectrum antibiotics
- To: septic shock

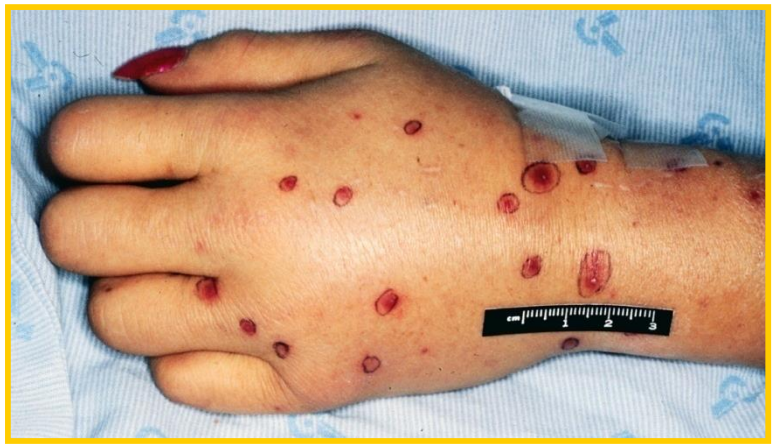
Deep seated IC

- Symptoms and signs depending on the affected organ / system

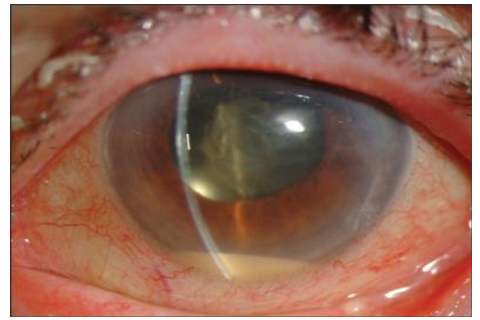
Sipsas NV, et al. Cancer 2009; 115:4745-52.

Διηθητική καντιντίαση
Φάσμα κλινικών εκδηλώσεων

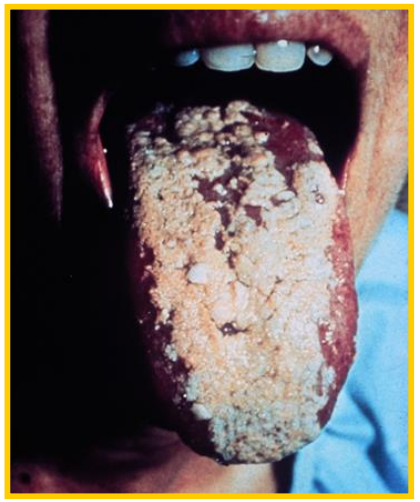
Δερματικές εκδηλώσεις μυκηταιμίας



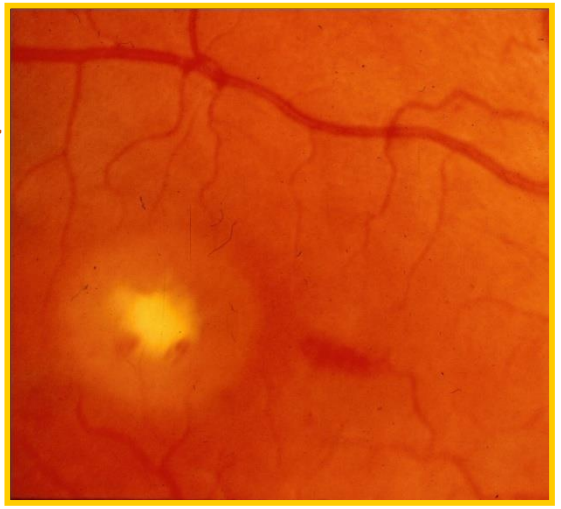
Ενδοφθαλμίτιδα



Στοματίτιδα

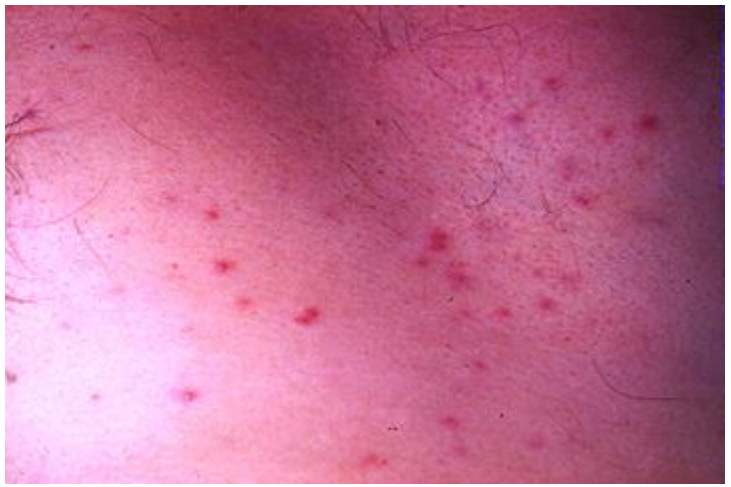


Χοριο-αμφιβληστροειδίτιδα



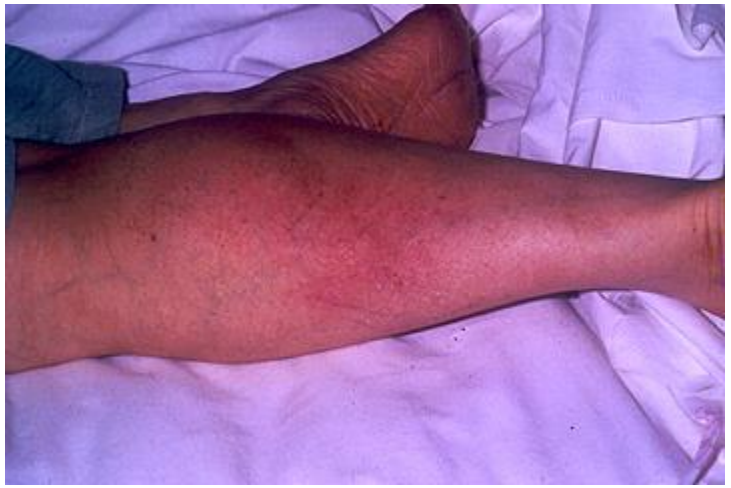
Walsh et al. Infect Dis Clin North Am. 1996;10:365-400.

Skin lesions of disseminated candidiasis



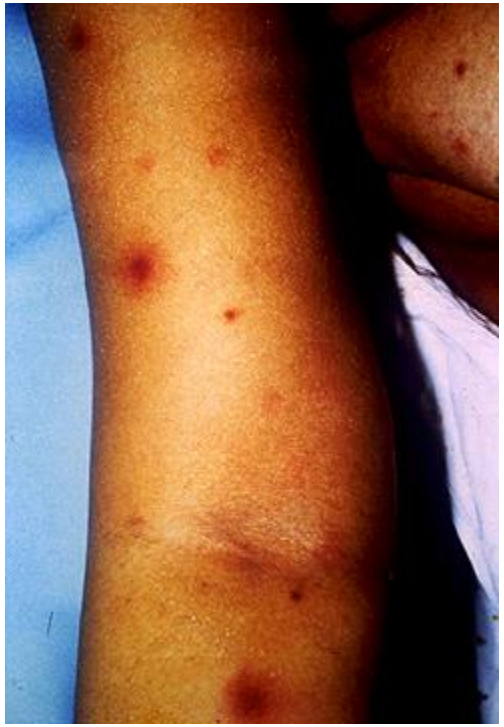
Tiny pustular lesions due to the hematogenous dissemination of Candida albicans can be seen in this hospitalized patient with fever and signs of sepsis.

Muscle abscess in disseminated candidiasis



Erythematous, warm, tender gastrocnemius muscle in an elderly man with acute leukemia and neutropenia. Biopsy showed microabscesses containing budding yeasts and pseudohyphae.

Nodules in disseminated candidiasis



Large erythematous, nodular lesions with central necrosis in a patient with acute leukemia and disseminated candidiasis.

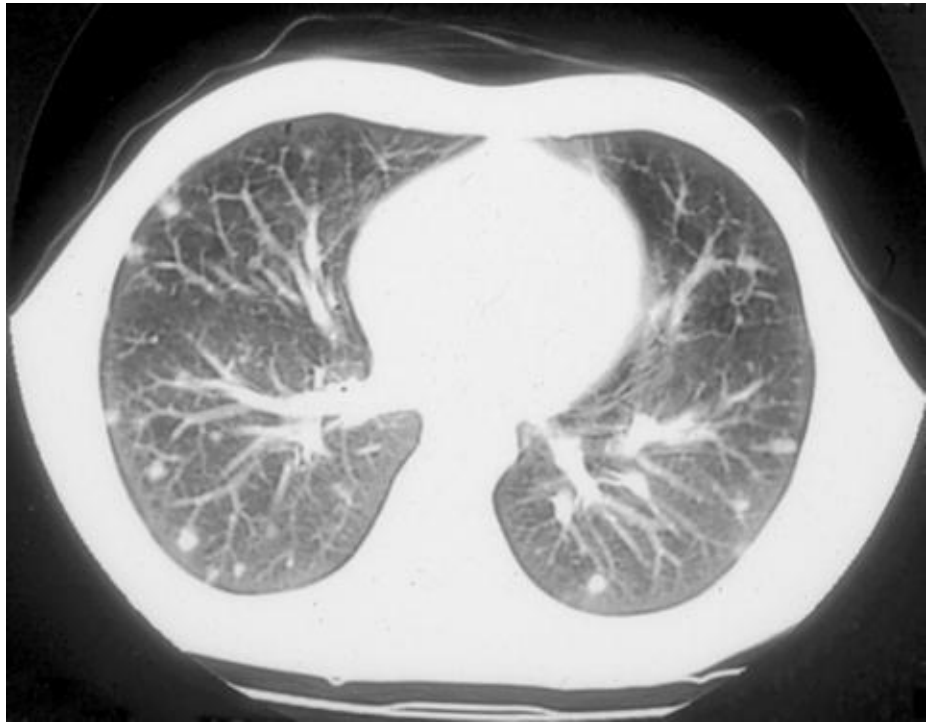
Pulmonary IC

CT scan: multiple peripheral small nodules

Candida colonization in the airway is extremely common in ICU

Candida pneumonia is rare

Candida-positive culture of respiratory secretions should NOT be used as an indication to initiate AF therapy



Kontoyiannis DP, et al. Clin Infect Dis. 2002;34: 400-403.
Wood GC, et al. Intensive Care Med. 2006;32: 599-603.

Hepatosplenic candidiasis

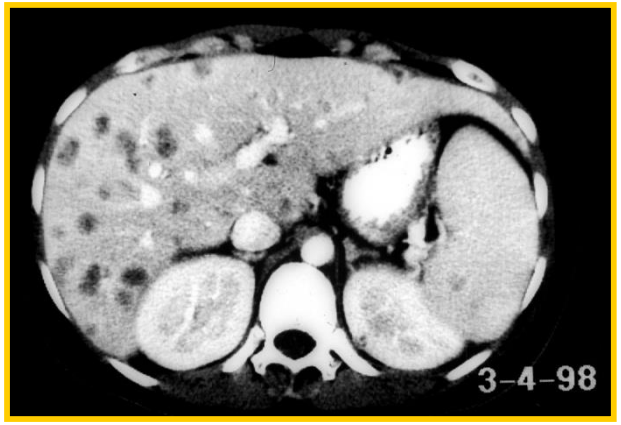
As a rule

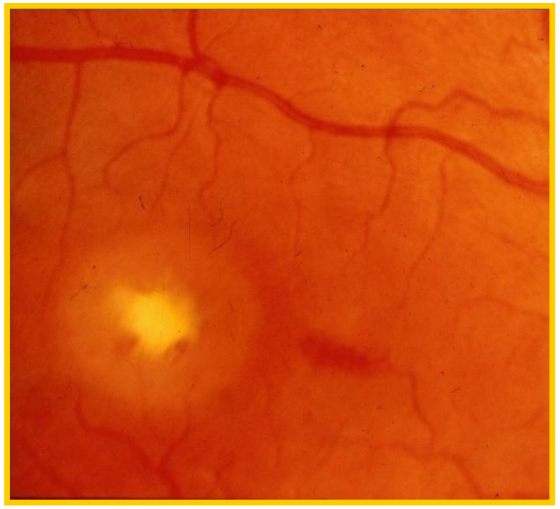
In every patient with candidemia

CT / US of liver - spleen

ophthalmologic exam

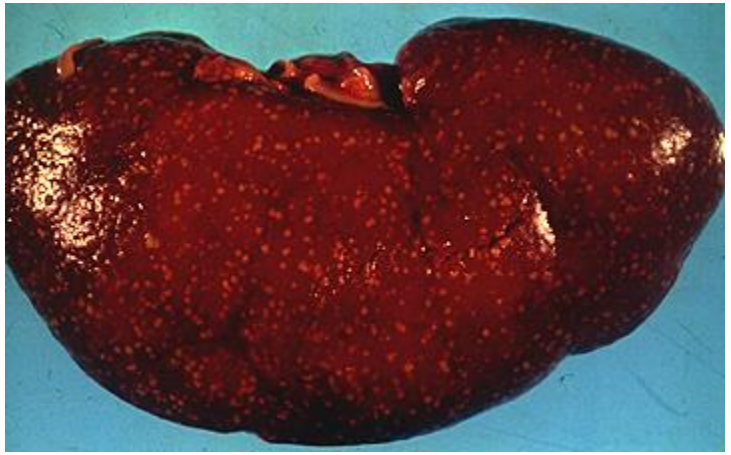
within first 7 days of diagnosis





Walsh T et al. Infect Dis Clin North Am. 1996;10:365-400.

Disseminated candidiasis kidney



Numerous small abscesses can be seen studding the surface of the kidney in a patient who developed disseminated candidiasis during a chloramphenicol-induced neutropenia.

Διάγνωση

Καλλιέργεια αίματος

Μόνο 35%-50% έχουν θετική καλλιέργεια κατά την έναρξη των συμπτωμάτων

Η προφύλαξη μειώνει την ευαισθησία

> 72 ώρες για θετικοποίηση για *Candida*

Άλλες 48 ώρες για ταυτοποίηση – μυκητόγραμμα

- peptide nucleic acid fluorescence in situ hybridization (PNA FISH)
- direct germ tube analysis
- nucleic acid detection tests

Ορολογικές μέθοδοι

Ανιχνεύουν συστατικά του κυτταρικού τοιχώματος του μύκητα

- mannan
- β-(1,3)-D-glucan

Αντισώματα

- anti-mannan antibodies

Συνδυασμός

- mannan antigen / anti-mannan antibody

Μοριακές μέθοδοι

PCR assays

amplification of

the panbacterial [16S and 23S ribosomal RNA (rRNA)]

panfungal (28S rRNA)

intervening internal transcribed spacer (ITS) gene regions

Diagnosis

MALDI-TOF mass spectroscopy

Requires growth in culture

T2 magnetic resonance assay

the test uses whole blood without requiring growth in culture

allow rapid (< 5 hours) species identification with excellent sensitivity and specificity

Mylonakis E, et al. Clin Infect Dis 2015; 60:892
Clancy CJ, et al. Clin Infect Dis. 2018;66: 1678.

B-D-Glucan assay– Clinical Utility in the ICU

A meta-analysis that included 16 studies evaluating BDG for IFIs

pooled sensitivity was 77 % (95% CI 67-84 %)

pooled specificity was 85 % (95% CI 80-90 %)

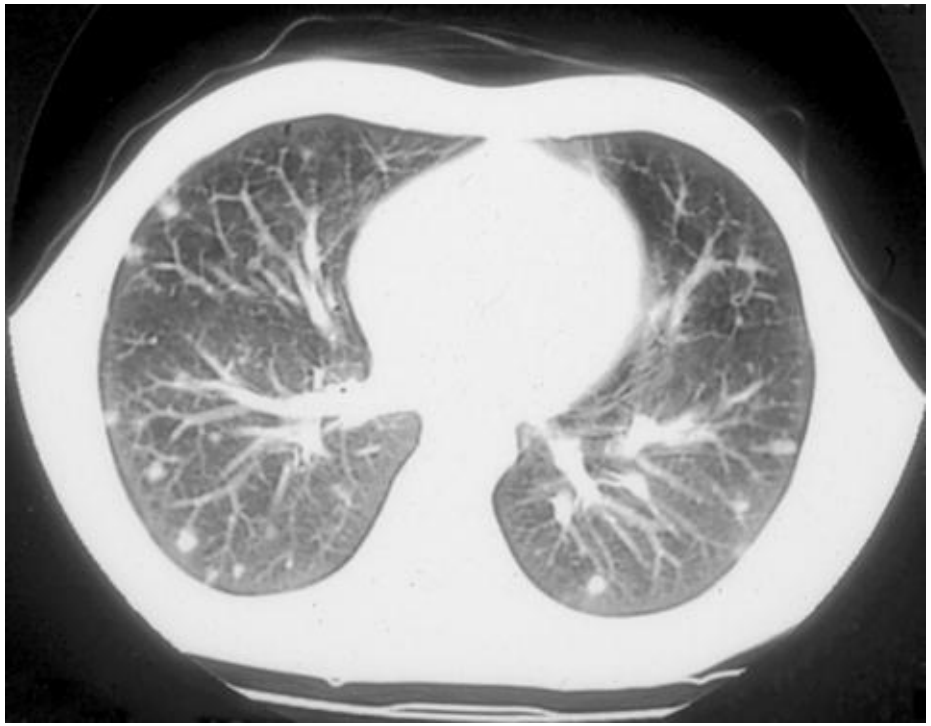
False-positive results are rare in healthy controls, but more common among patients in an ICU

In some cases can be used to monitor response to treatment

Karageorgopoulos DE, et al. Clin Infect Dis. 2011;52(6):750
Gupta P, et al. Mycoses 2017, 60, 2234–2240.
Lamoth F, Calandra T. J Antimicrob Chemother 2017, 72, i19–i28.
Wheat LJ. *Clin Chest Med* 2009; 30:367–77

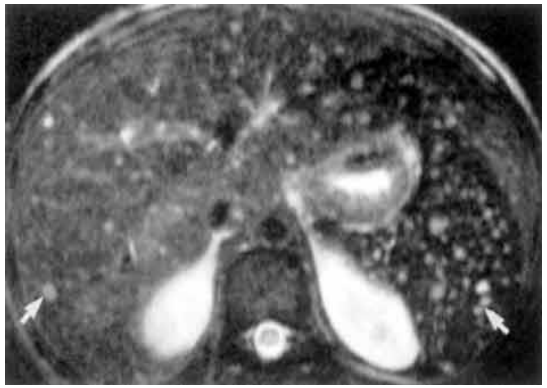
CT

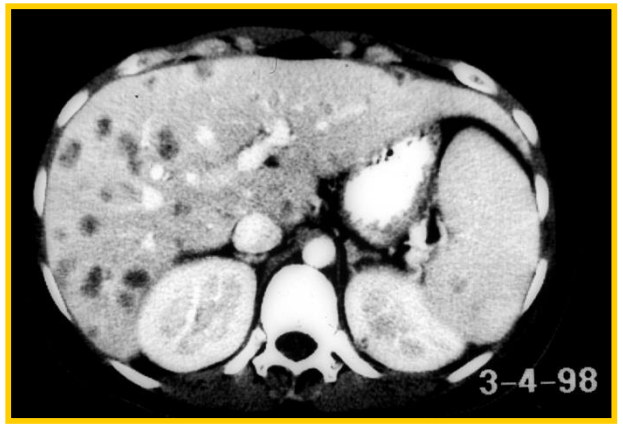
CT scan of the thorax showing discrete nodules, which were a manifestation of chronic disseminated candidiasis after treatment for acute leukaemia.

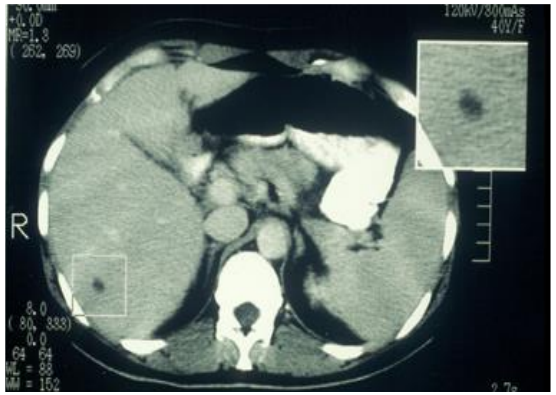


Radiologic Diagnosis in Hepatosplenic Candidiasis

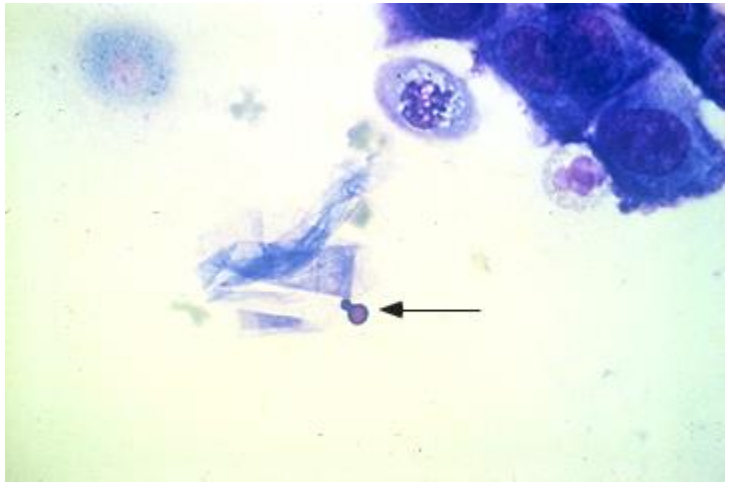
MRI and CT more sensitive than ultrasound: ~90% versus ~70%







Skin scraping in disseminated candidiasis



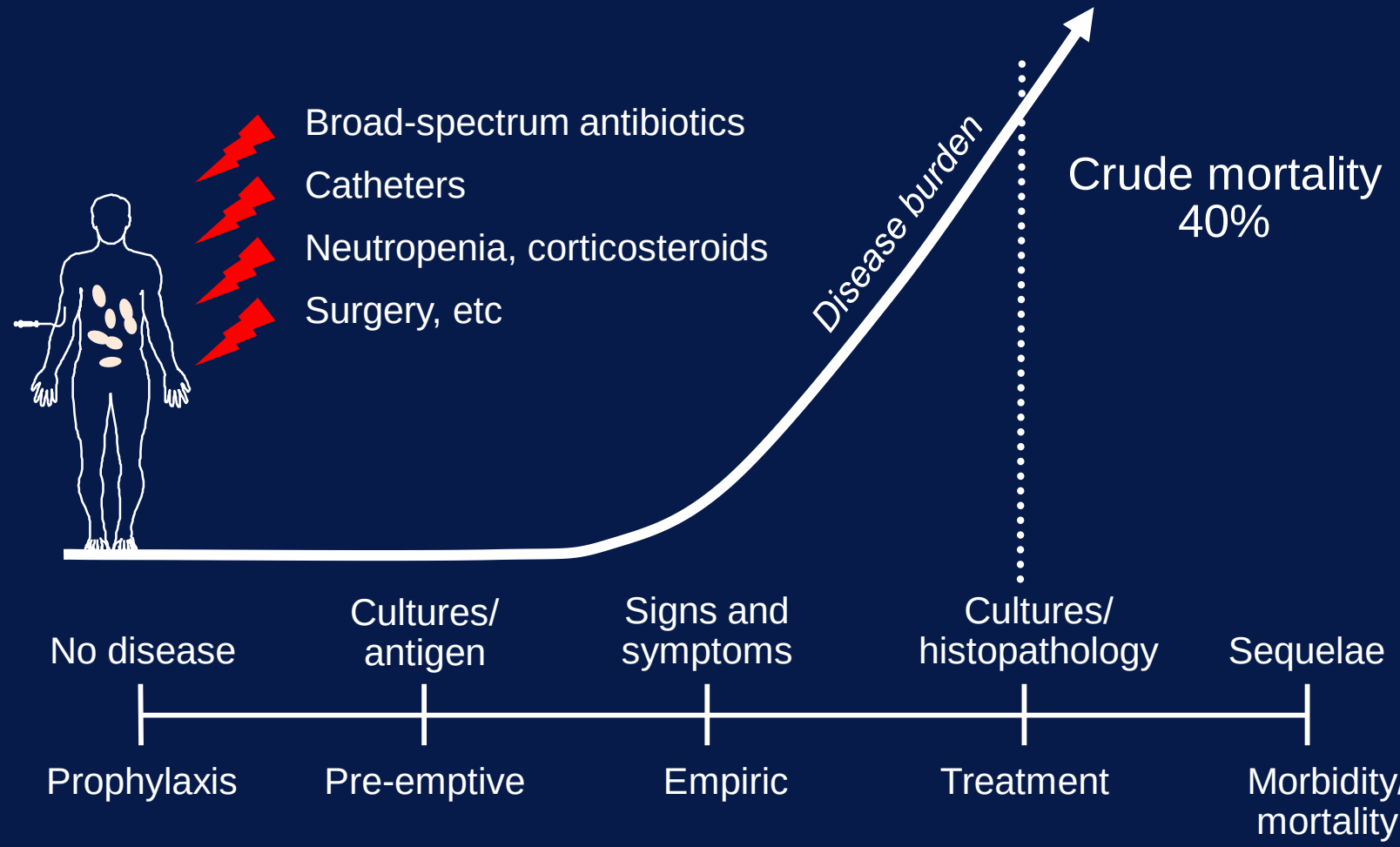
A budding yeast (arrow) is visible in this Gram stain of a pustular skin lesion from a neutropenic patient.

Θεραπεία

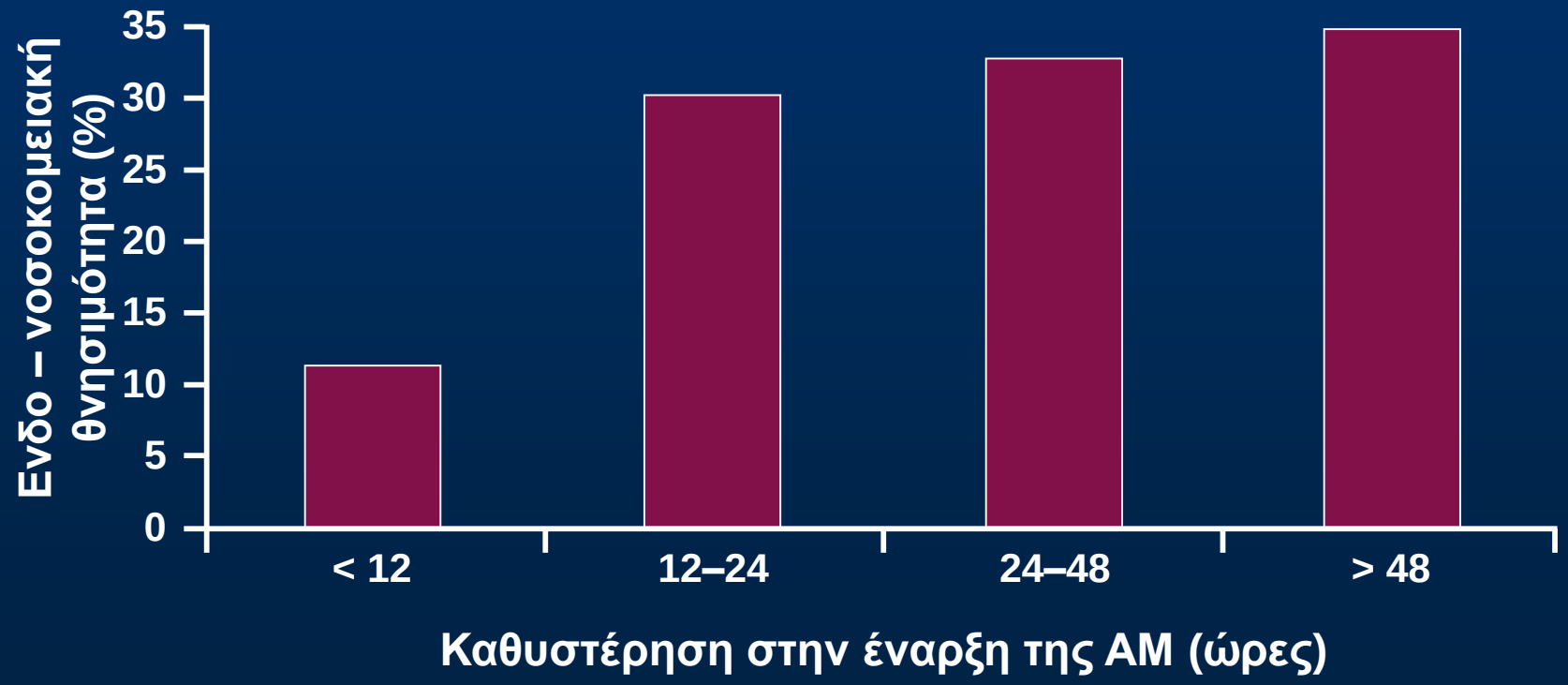
Αρχές

‘Εγκαιρα

Pathogenesis of Invasive Candidiasis



Σχέση μεταξύ θνησιμότητας και έγκαιρης έναρξης της ΑΜ αγωγής



Morrell M, *et al*. *Antimicrob Agents Chemother* 2005; **49:**3640 5

Ανάλογα με το είδος της Candida

Susceptibility profile of *Candida* species

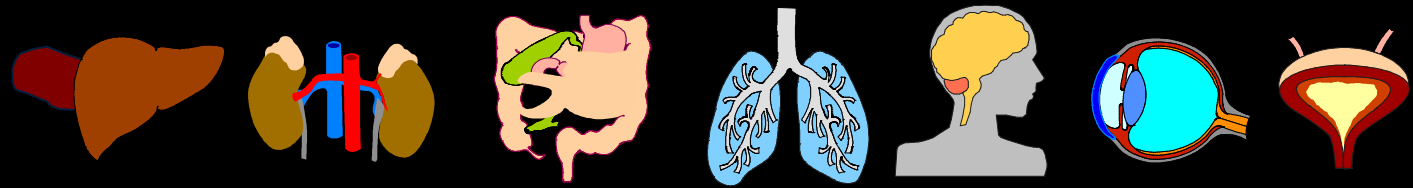
Candida sp	AMB[a]	FLUC	ITRA	VOR	Echinocandin
C albicans	S	S	S	S	S
C tropicalis	S	S	S	S	S
C parapsilosis	S	S	S	S	S-NS
C glabrata	S-I	S-DD-R	S-DD-R	S-S-DD	S
C krusei	S-I	R	S-DD-R	S	S
C lusitaniae	S-R	S	S	S	S

[a]No established breakpoints.

Adapted from Pappas et al. *Clin Infect Dis.* 2004;38:161-189.

Ανάλογα με το σημείο της λοίμωξης

Antifungal Pharmacokinetics: Drug Distribution



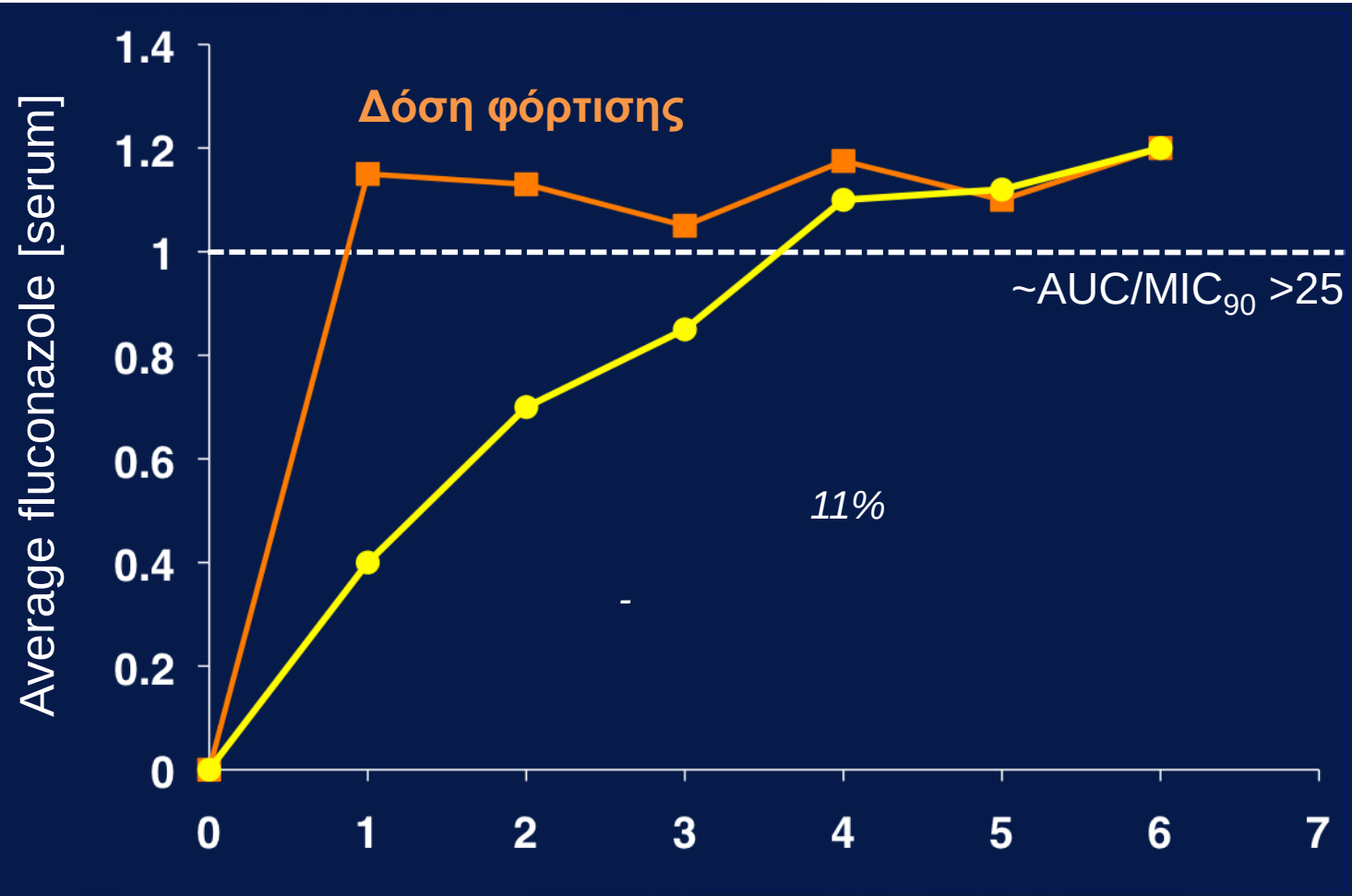
	Liver/ Spleen	Kidneys	Gut/Gall Bladder	Lung	Brain/ CSF	Eye	Urine/ Bladder
AmB	+	+	+	+	-		-
5FC	+	+	+	+	+	+	+
FLU	+	+	+	+	+	+	+
ITR	+	+	+	+	-		-
VOR	+	+	+	+	+	+	
POS	+	+	+	+	-		
Echino	+	+	+	+	-		

+ ≥50% of serum concentrations
– <10% of serum concentrations

Groll AH et al. *Advances in Pharmacol.* 1998;44:343.

ΑΜ στην κατάλληλη δόση

Επίπεδα της φλουκοναζόλης στον ορό με ή χωρίς δόση φόρτισης



AUC = area under the curve.

Goa KL, Barradell LB. *Drugs*. 1995;50:658-690.

Απομάκρυνση του κεντρικού καθετήρα

IDSA guidelines

IDSA recommendations

IV catheter removal strongly recommended for non-neutropenic patients (A-III)

Data for catheter removal in neutropenic patients less compelling, however experts recommend removal of CVCs (including tunneled catheters) for patients with persistent candidemia in whom it is logistically feasible (B-III)

CVC?

Σε πρόσφατη μελέτη η έγκαιρη αφαίρεση του CVC (σε 24 ή 48 h μετά την έναρξη της θεραπείας) σε 842 ασθενείς με καντινταιμία δεν βελτίωσε την πρόγνωση

Nucci M, Anaissie E, Betts RF, et al.: Early removal of central venous catheter in patients with candidemia does not improve outcome: analysis of 842 patients from 2 randomized clinical trials. Clin Infect Dis 2010, 51:295-303.

Impact of therapy on mortality across *Candida* spp: A patient-level analysis of randomized controlled clinical trials

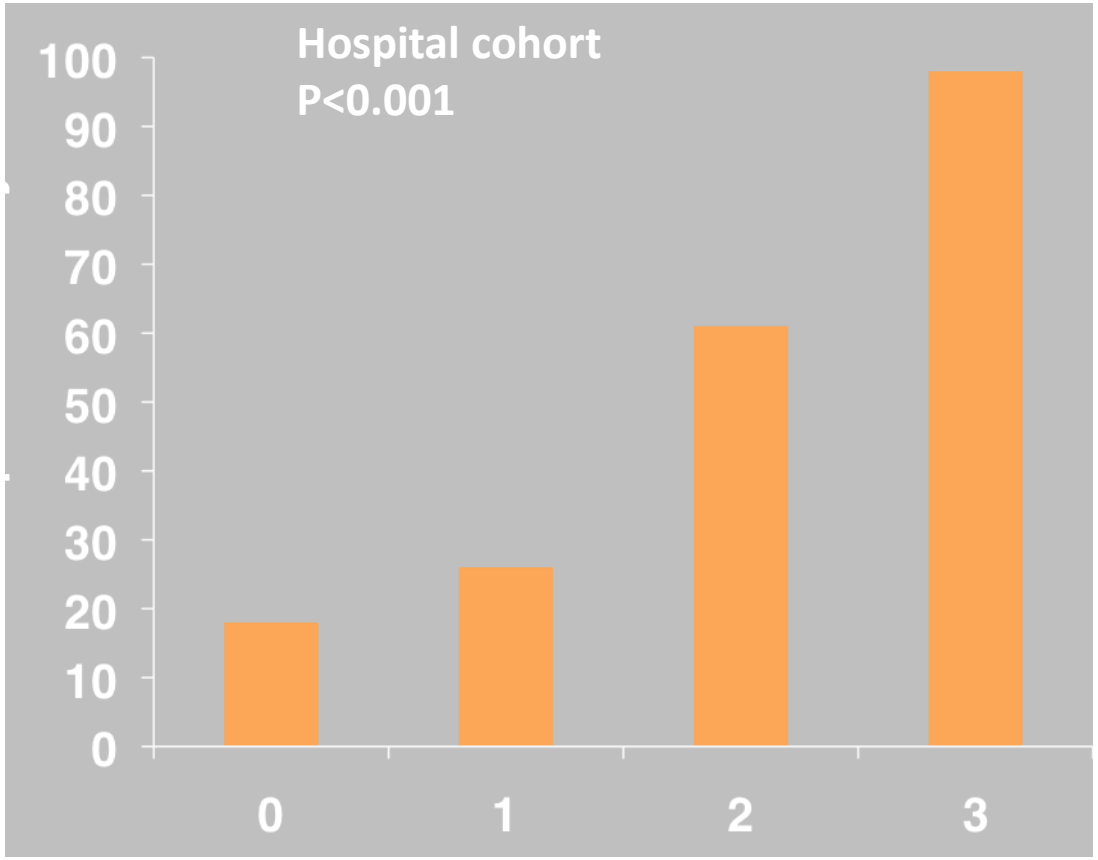
Risk factor	OR	95% CI	P value
Age	**1.01**	**1-1.02**	**0.02**
Apache II	**1.11**	**1.08-1.14**	**0.0001**
Immunosuppressive meds.	**1.69**	**1.08-2.44**	**0.01**
C. tropicalis	**1.64**	**1.10-2.44**	**0.01**
Removal of CVC	**0.49**	**0.34-0.70**	**0.0001**
Use of an echinocandin	**0.39**	**0.20-0.78**	**0.02**

No impact of fluconazole-resistant species (e.g., *C. glabrata*)

Effect of cumulative risk factors

Risk factors:

- **Delayed Rx (24 hour)**
- **Retain CVC**
- **Inadequate dosing (fluconazole)**



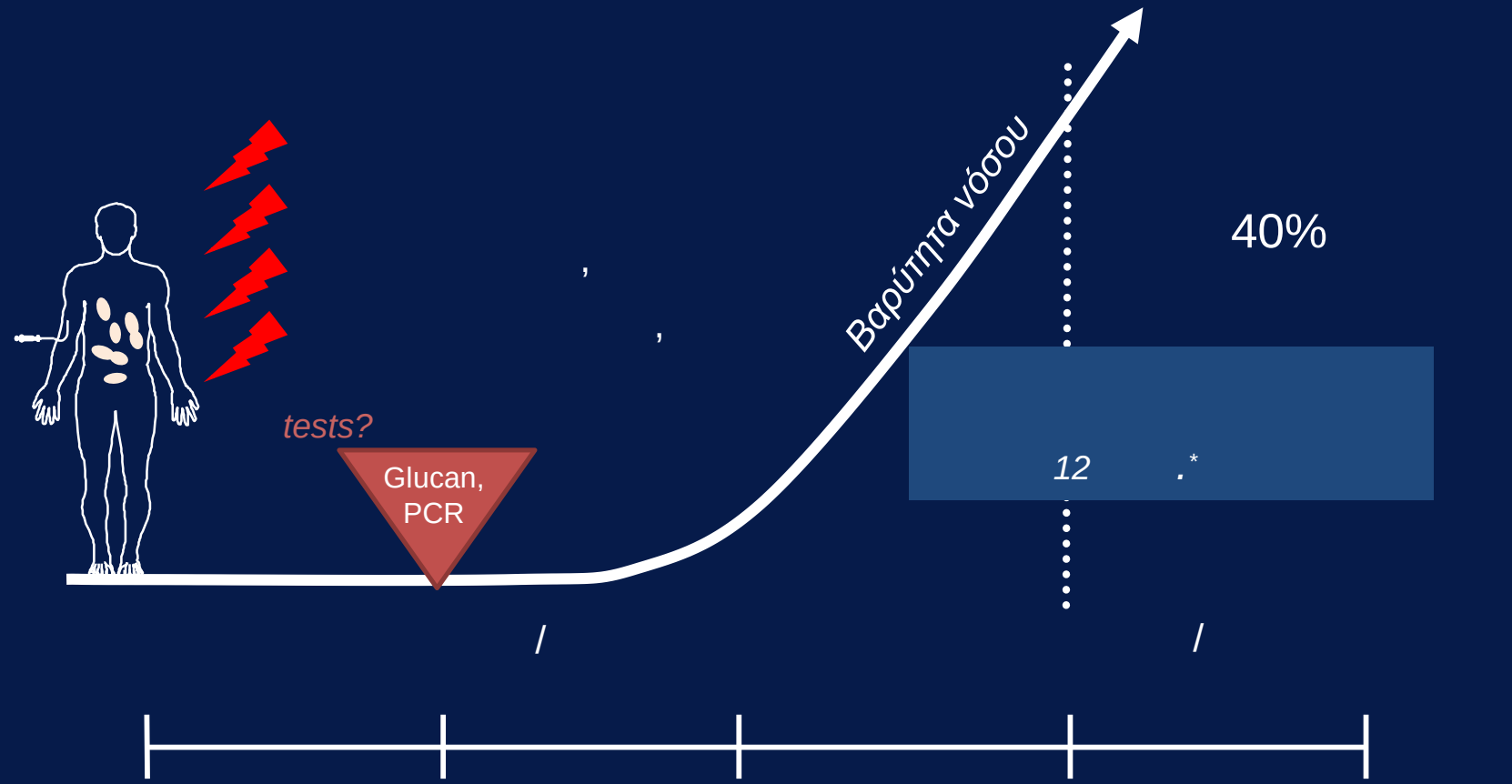
Early treatment strategies for IC

Prophylaxis

Empirical therapy

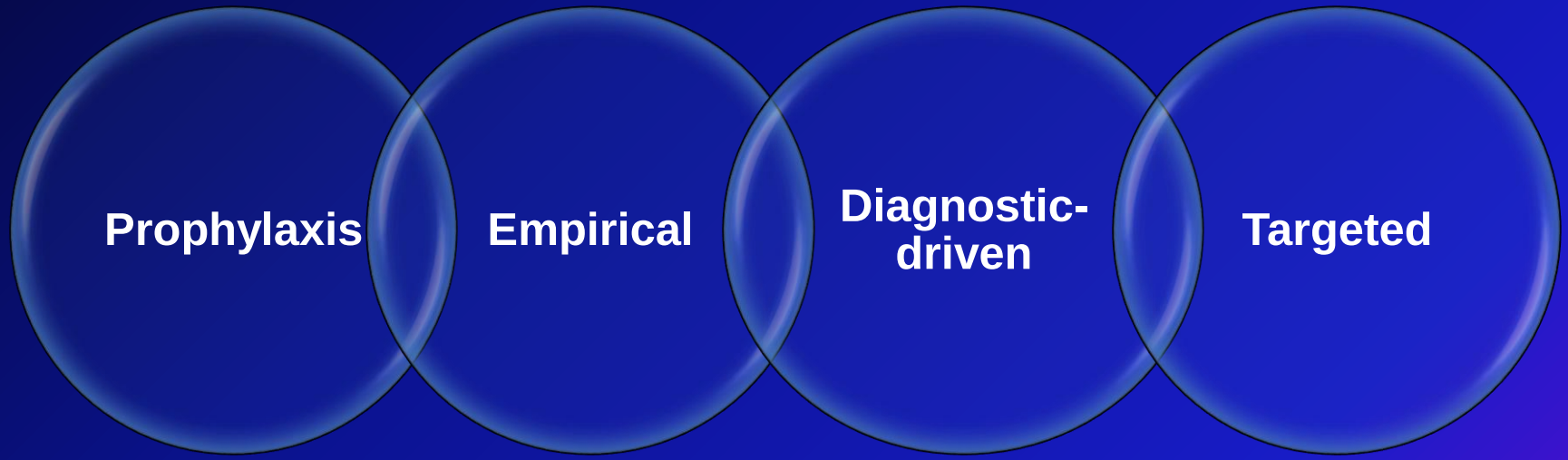
Targeted therapy

Συστηματική καντιντίαση



PCR = polymerase chain reaction.
*Morrell M et al. *Antimicrob Agents Chemother.* 2005;49:3640-3645.

Strategies not Mutually Exclusive



Προφύλαξη

Προφύλαξη

- Επειδή η ΣΚ έχει μεγάλη θνησιμότητα και δεν υπάρχουν ικανοποιητικά διαγνωστικά τέστ
  - Η προφύλαξη είναι μια ελκυστική στρατηγική

- Κλινικές μελέτες έδειξαν μείωση στην συχνότητα και τη θνησιμότητα της ΣΚ στους αιματολογικούς ασθενείς

Early antifungal intervention strategies

- Για να προλάβουμε μια λοίμωξη από *Candida* στη ΜΕΘ πρέπει να δώσουμε προφύλαξη σε 94 ασθενείς
  - Playford EG, et al. Antifungal agents for preventing fungal infections in non-neutropenic critically ill patients.
    Cochrane Database Syst Rev 2006, 1: CD004920
- Οι υπόλοιποι 93 ;

Early antifungal intervention strategies

- Κατάχρηση των αντιμυκητιασικών οδηγεί σε αντοχή
  - Rocco TR, et al. Effects of fluconazole administration in critically ill patients: analysis of bacterial and fungal resistance.
    Arch Surg. 2000;135:160-5.
- Μείωση της χρήσης προφύλαξης ελαττώνει τη συχνότητα των non-albicans *Candida* spp
  - Bassetti M, et al. Incidence of candidaemia and relationship with fluconazole use in an intensive care unit.
    J Antimicrob Chemother. 2009;64:625-9.

Prediction rules

- Για να ανιχνευθούν οι ασθενείς με τον μέγιστο κίνδυνο για ΣΚ
  - Αναπτύχθηκαν προγνωστικοί κανόνες

- Based on
  - Colonization
  - Clinical factors

Colonization index

- the number of distinct body sites colonized by *Candida* spp. divided by the total number of distinct sites tested per patient

- CIs ≥ 0.5 = high risk for IC.

    - Pittet *et al. Annals of Surgery* 1994; 220:751-758.

Mycoses Study Group Rule

Use of the following during days 1-3 of ICU admission:

Mechanical ventilation *AND* central venous catheter *AND* any broad-spectrum antibiotics (active vs ≥2 bacterial classes)

AND at least 1 of the following risk factors:

Use of parenteral nutrition on days 1-3 of ICU admission

Any type of dialysis on days 1-3 of ICU admission

Any major surgery (performed with general anesthesia) within 7 days of ICU admission

Diagnosis of pancreatitis (by CT or lipase >1000 U/L) within 7 days of ICU admission

Use of systemic steroids (>1 dose of prednisone equivalent to ≥20 mg/day) within 7 days of ICU admission

Use of any other immunosuppressive agent (>1 dose) within 7 days of ICU admission

Ostrosky-Zeichner et al. Presented at: 46th ICAAC; San Francisco, 2006. Abstract M-883.

Prediction rules - Candida score

- Candida score (rounded)
  - Multifocal colonization: 1
  - Surgery: 1
  - Severe sepsis: 2
  - TPN: 1

- Performance
  - Score >2.5

    RR = 7.75

    Sensitivity = 0.81

    Specificity = 0.74

- Select patients who would benefit from early antifungal treatment.

León et al. Crit Care Med. 2006;34:730-737.

Πρώιμη / εμπειρική αγωγή

Pre-emptive
Empirical treatment

Ποιοι ασθενείς;

- Κάθε ασθενής υψηλού κινδύνου για ΣΚ, που έχει:
  - Πυρετό που δεν ανταποκρίνεται σε αντιβιοτικά ευρέως φάσματος
  - Καμιά άλλη σαφή αιτία πυρετού
    - λοίμωξη από πολυανθεκτικό μικρόβιο
    - CMV
    - νεοπλασματικό ή φαρμακευτικό πυρετό
  - Αποικισμένος με *Candida*

Που θα βασιστούμε;

- Κλινική εκτίμηση
- Παράγοντες κινδύνου
- Ορολογικοί δείκτες ΣΚ
- Αποικισμός

Annals of Internal Medicine | ARTICLE

Empirical Fluconazole versus Placebo for Intensive Care Unit Patients

A Randomized Trial

Mindy G. Schuster, MD; John E. Edwards Jr., MD; Jack D. Sobel, MD; Rabih O. Darouiche, MD; Adolf W. Karchmer, MD; Susan Hadley, MD; Gus Slotman, MD; Helene Panzer, PhD; Pinaki Biswas, PhD; and John H. Rex, MD

Background: Invasive infection with *Candida* species is an important cause of morbidity and mortality in intensive care unit (ICU) patients. Optimal preventive strategies have not been clearly defined.

Objective: To see whether empirical fluconazole improves clinical outcomes more than placebo in adult ICU patients at high risk for invasive candidiasis.

Design: Double-blind, placebo-controlled, randomized trial conducted from 1995 to 2000.

Setting: 26 ICUs in the United States.

Patients: 270 adult ICU patients with fever despite administration of broad-spectrum antibiotics. All had central venous catheters and an Acute Physiology and Chronic Health Evaluation II score greater than 16.

Intervention: Patients were randomly assigned to either intravenous fluconazole, 800 mg daily, or placebo for 2 weeks and were followed for 4 weeks thereafter. Two hundred forty-nine participants were available for outcome assessment.

Measurements: A composite primary outcome that defined success as all 4 of the following: resolution of fever; absence of invasive fungal infection; no discontinuation because of toxicity; and no need for a nonstudy, systemic antifungal medication (as assessed by a blinded oversight committee).

Results: Only 44 of 122 (36%) fluconazole recipients and 48 of 127 (38%) placebo recipients had a successful outcome (relative risk, 0.95 [95% CI, 0.69 to 1.32; $P = 0.78$]). The main reason for failure was lack of resolution of fever (51% for fluconazole and 57% for placebo). Documented invasive candidiasis occurred in 5% of fluconazole recipients and 9% of placebo recipients (relative risk, 0.57 [CI, 0.22 to 1.49]). Seven (5%) fluconazole recipients and 10 (7%) placebo recipients had adverse events resulting in discontinuation of the study drug. Discontinuation because of abnormal liver test results occurred in 3 (2%) fluconazole recipients and 5 (4%) placebo recipients.

Limitations: Twenty-one randomly assigned patients were not included in the analysis because they either did not meet entry criteria or did not have postbaseline assessments. Fewer fungal infections than anticipated occurred in the control group. Confidence bounds were wide and did not exclude potentially important differences in outcomes between groups.

Conclusion: In critically ill adults with risk factors for invasive candidiasis, empirical fluconazole did not clearly improve a composite outcome more than placebo.

Ann Intern Med. 2008;149:83-90. www.annals.org

For author affiliations, see end of text.

Στοχευμένη θεραπεία

Κλινικές μελέτες στην καντινταιμία

Study	Design	Success rate (cured + improved)
Mora-Duarte et al, 2002	Caspofungin vs. amphotericin B	73% vs. 62% * p = ns
Betts et al, 2006	Micafungin vs. caspofungin	74% (100 mg) 70% (150 mg) vs. 71% * p = ns
Kuse et al, 2007	Micafungin vs. liposomal amphotericin B	74% vs. 70% * p = ns
Reboli et al, 2005	Anidulafungin vs. fluconazole	76% vs. 60% ** p < o.o5

Mora-Duarte J et al. *N Engl J Med*. 2002;347:2020-2029.
Betts RF et al. 2006.
Kuse E-R et al. *Lancet*. 2007;369:1519-1527.
Reboli AC et al. *N Engl J Med.* 2007;356:2472-2482.

Clinical Infectious Diseases

IDSA GUIDELINE

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. Sobel[12]

Prophylaxis (*weak recommendation)*

Fluconazole, could be used in high-risk patients in adult ICUs with a high rate (>5%) of invasive candidiasis

(weak recommendation; moderate-quality evidence).

An alternative is to give an echinocandin

(weak recommendation; low-quality evidence).

Daily bathing of ICU patients with chlorhexidine, could be considered

(weak recommendation; moderate-quality evidence).

No effect on overall mortality

Papas PG et al. Clin Infect Dis 2016; 62(4):e1–50

What Is the Role of Empiric Treatment for Suspected Invasive Candidiasis in the ICU?

Empiric antifungal therapy should be considered in critically ill patients with fever

with risk factors for invasive candidiasis

no other known cause of fever

should be based on:

clinical assessment,

surrogate markers for invasive candidiasis,

and/or culture data from nonsterile sites

(strong recommendation; moderate-quality evidence).

Papas PG et al. Clin Infect Dis 2016; 62(4):e1–50

What Is the Role of Empiric Treatment for Suspected Invasive Candidiasis in the ICU?

Empiric antifungal therapy should be started as soon as possible in patients

who have the above risk factors and

who have clinical signs of septic shock

(strong recommendation; moderate-quality evidence)

Preferred empiric therapy for suspected candidiasis in non-neutropenic patients in the intensive care unit (ICU) is an echinocandin

(strong recommendation; moderate-quality evidence)

Papas PG et al. Clin Infect Dis 2016; 62(4):e1–50

What Is the Role of Empiric Treatment for Suspected Invasive Candidiasis in the ICU?

Fluconazole, is an acceptable alternative for patients who

have had no recent azole exposure and

are not colonized with azole-resistant *Candida* species

(strong recommendation; moderate-quality evidence).

Lipid formulation AmB, 3–5 mg/kg daily, is an alternative if there is intolerance to other antifungal agents

(*strong recommendation; low-quality evidence)*.

Recommended duration of empiric therapy for suspected invasive candidiasis in those patients who improve is 2 weeks

(weak recommendation; low-quality evidence).

Papas PG et al. Clin Infect Dis 2016; 62(4):e1–50

What Is the Treatment for documented Candidemia in ICU Patients?

An echinocandin is recommended as initial therapy

(strong recommendation; high-quality evidence).

Fluconazole, intravenous or oral, is an acceptable alternative in selected patients,

who are not critically ill

who are considered unlikely to have a fluconazole resistant *Candida* species

(strong recommendation; high-quality evidence)

Voriconazole 400 mg offers little advantage over fluconazole as initial therapy

(strong recommendation; moderate-quality evidence).

Papas PG et al. Clin Infect Dis 2016; 62(4):e1–50

What Is the Treatment for documented Candidemia in Non-neutropenic Patients?

- Lipid formulation amphotericin B (AmB) (3–5 mg/kg daily) is a reasonable alternative if there is:
  - intolerance,
  - limited availability, or
  - resistance to other antifungal agents
  - *(strong recommendation; high-quality evidence)*.
- Recommended duration of therapy for candidemia without obvious metastatic complications is for 2 weeks
  - after documented clearance of *Candida* species from the bloodstream
  - resolution of symptoms attributable to candidemia
  - *(strong recommendation; moderate-quality evidence)*.

Papas PG et al. Clin Infect Dis 2016; 62(4):e1–50

Table 4: ECIL-6 recommendations for initial first-line treatment of candidemia

	Overall population	Hematological patients
Antifungal therapy		
- Micafungin [a]	A I	A II
- Anidulafungin	A I	A II [b]
- Caspofungin	A I	A II
- Liposomal amphotericin B	A I	A II
- Amphotericin B lipid complex	B II	B II
- Amphotericin B colloidal dispersion	B II	B II
- Amphotericin B deoxycholate [c]	C I	C II
- Fluconazole [d,e]	A I	C III
- Voriconazole [d]	A I	B II
Catheter removal [f]	A II	B II

[a] See warning box in European label; [b] Provisional grading; [c] Close monitoring for adverse event is required ; [d] Not in severely ill unstable patients; [e] Not in patients with previous azole exposure; [f] if the catheter cannot be removed, use of an echinocandin or a lipid formulation of amphotericin B is recommended.

Tissot F, et al. Hematologica 2017;

Table 5: ECIL-6 recommendations for first-line treatment of candidemia after species identification

Candida species	Overall population		Hematological patients	
C. albicans	Echinocandins [a]	A I	Echinocandins	A II
	Fluconazole [b]	A I	Fluconazole	C III
	Liposomal amphotericin B	A I	Liposomal amphotericin B	B II
	Amphotericin B lipid complex	A II	Amphotericin B lipid complex	B II
	Amphotericin B colloidal dispersion	A II	Amphotericin B colloidal dispersion	B II
	Amphotericin B deoxycholate	C I	Amphotericin B deoxycholate	C II
C. glabrata	Echinocandins [a]	A I	Echinocandins	A II
	Liposomal amphotericin B	B I	Liposomal amphotericin B	B II
	Amphotericin B lipid complex	B II	Amphotericin B lipid complex	B II
	Amphotericin B colloidal dispersion	B II	Amphotericin B colloidal dispersion	B II
	Amphotericin B deoxycholate	C I	Amphotericin B deoxycholate	C II
C. krusei	Echinocandins [a]	A II	Echinocandins [a]	A III
	Liposomal amphotericin B	B I	Liposomal amphotericin B	B II
	Amphotericin B lipid complex	B II	Amphotericin B lipid complex	B II
	Amphotericin B colloidal dispersion	B II	Amphotericin B colloidal dispersion	B II
	Amphotericin B deoxycholate	C I	Amphotericin B deoxycholate	C II
Oral stepdown	Voriconazole	B I	Voriconazole	C III
C. parapsilosis	Fluconazole	A II	Fluconazole	A III
	Echinocandins [c]	B II	Echinocandins	B III

[a] same grading for anidulafungin, caspofungin, micafungin ; [b] not in severely ill patients; [c] if echinocandin-based regimen introduced before species identification and patient responding clinically and microbiologically (sterile blood cultures at 72h), continuing use of echinocandin might be considered

Tissot F, et al. Hematologica 2017;

Απομάκρυνση του κεντρικού καθετήρα

IDSA guidelines

IDSA recommendations

IV catheter removal strongly recommended for non-neutropenic patients (A-III)

Data for catheter removal in neutropenic patients less compelling, however experts recommend removal of CVCs (including tunneled catheters) for patients with persistent candidemia in whom it is logistically feasible (B-III)

CVC?

Σε πρόσφατη μελέτη η έγκαιρη αφαίρεση του CVC (σε 24 ή 48 h μετά την έναρξη της θεραπείας) σε 842 ασθενείς με καντινταιμία δεν βελτίωσε την πρόγνωση

Nucci M, Anaissie E, Betts RF, et al.: Early removal of central venous catheter in patients with candidemia does not improve outcome: analysis of 842 patients from 2 randomized clinical trials. Clin Infect Dis 2010, 51:295-303.

IDSA Clinical Practice Guideline 2016

The echinocandins have emerged as preferred agents for most episodes of candidemia and invasive candidiasis,

with the exception of central nervous system, eye, and urinary tract infections

This preference is based on:

a strong safety profile,

convenience,

early fungicidal activity,

a trend toward better outcomes

the emergence of azole-resistant *Candida* species.

Papas G et al. Clin Infect Dis 2016; 62(4):e1–50

Factors affecting mortality in IC

Meta-analysis of 7 Randomized trials, n= 1831 patients

Risk factor	OR	95% CI	P value
Age	1.01	1-1.02	0.02
Apache II	1.11	1.08-1.14	0.0001
Immunosuppressive meds.	1.69	1.08-2.44	0.01
C. tropicalis	1.64	1.10-2.44	0.01
Removal of CVC	0.49	0.34-0.70	0.0001
Use of an echinocandin	0.39	0.20-0.78	0.02

Andes DR, et al.: [abstract M-1312]. Presented at the 50th ICAAC, Boston, USA; September 12-15, 2010

Θεραπεία καντιντουρίας

ΔΕΝ την θεραπεύουμε εκτός αν υπάρχουν παράγοντες κινδύνου

Ποιους θεραπεύουμε

- Symptomatic patients
- Neutropenic patients
- Low birth-weight infants
- Patients with urological manipulations/obstruction

- **Θεραπεία**
  - Remove “hardware” (stents and/or Foley)
  - Fluconazole (200–400 mg/d)
  - Flucytosine (100 mg/kg/d)
  - Lower urinary tract infections: AmB bladder irrigations (rarely useful)[1]
  - Upper urinary tract infections (pyelonephritis): can use azoles and echinocandins[2,3]

Drew RH et al. *Clin Infect Dis*. 2005;40:1465-1470.[1] Sobel JD et al. *Clin Infect Dis*. 2007;44:e46-e49.[2]
Pappas PG et al. *Clin Infect Dis*. 2009;48:503-535.[3]

Κλινική σημασία καντιντουρίας

mycoses
Diagnosis, Therapy and Prophylaxis of Fungal Diseases

Original article

Candiduria in haematologic malignancy patients without a urinary catheter: nothing more than a frailty marker?

Sarah P. Georgiadou,[1] Jeffrey Tarrand,[2] Nikolaos V. Sipsas[3] and Dimitrios P. Kontoyiannis[1]

[1]Department of Infectious Diseases, Infection Control and Employee Health, The University of Texas MD Anderson Cancer Center, Houston, TX, USA, [2]Department of Laboratory Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX, USA and [3]Infectious Diseases Unit, Pathophysiology Department, Laikon General Hospital and Medical School, National and Kapodistrian University of Athens, Athens, Greece

Κλινική σημασία καντιντουρίας

- Candidemia and crude mortality rates at 4 weeks were low (4% and 12% respectively).
- Isolated candiduria in patients with haematologic malignancies
  - has risk factors similar to those in other hospitalised patients,
  - it does not seem to be a strong predictor of subsequent invasive candidiasis.

ΕΞΑΤΟΜΙΚΕΥΣΗ

Η καλύτερη στρατηγική
(ιδιαίτερα στον αιματολογικό ασθενή)

Εξατομίκευση της θεραπείας