ΠΜΣ Λοιμώξεις

Συστηματική Καντιντίαση
Καντινταιμία

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ΓΝΑ « Λαϊκό»

Η συστηματική καντιντίαση: είναι σημαντική για τον κλινικό;

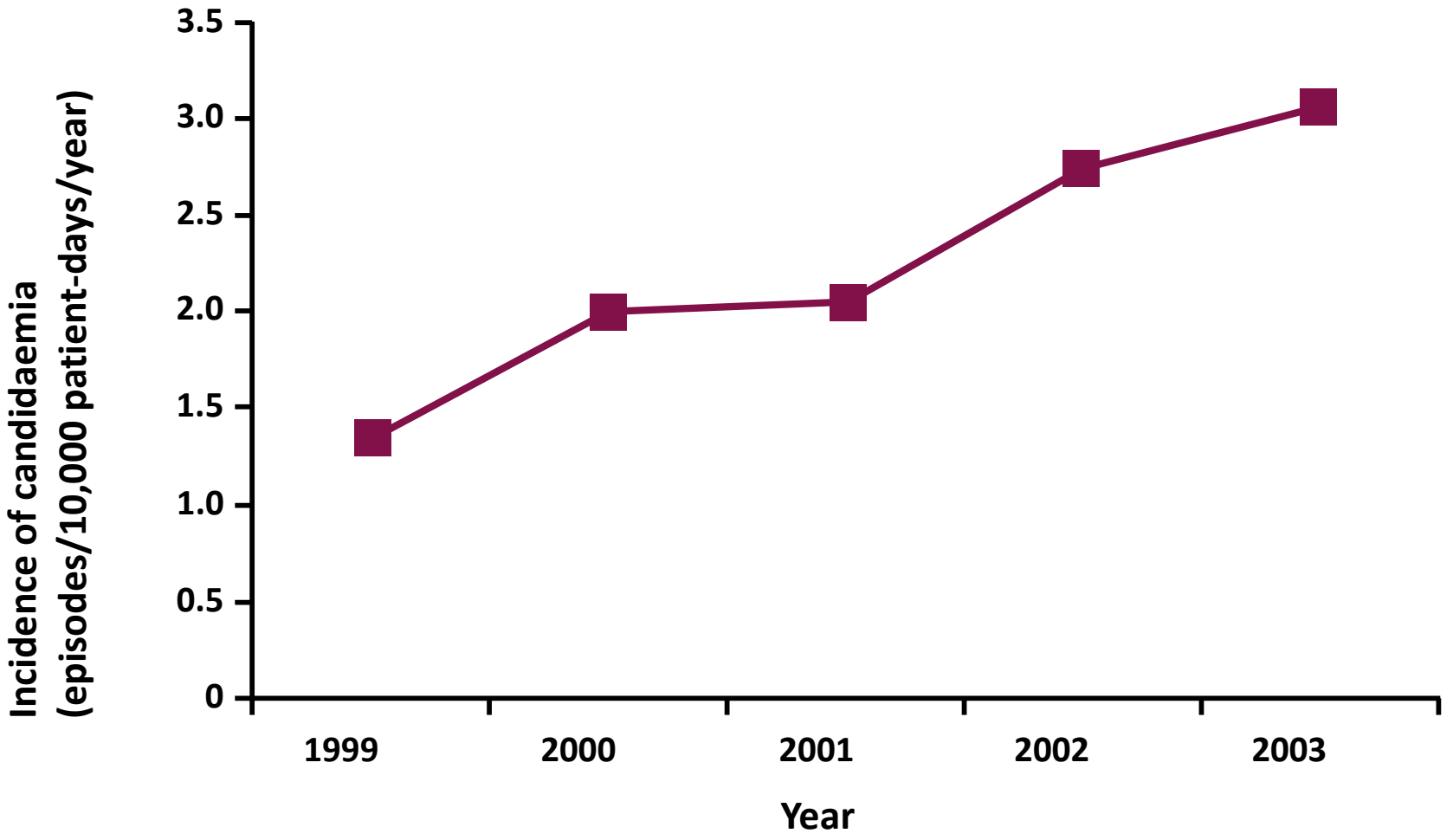
- Η συχνότητα της αυξάνει
- Έχει μεγάλη νοσηρότητα και θνησιμότητα
- Η επιδημιολογία της μεταβάλλεται
  - Non-albicans spp.
- Υπάρχει πρόβλημα αντοχής
- Νέα αντιμυκητιασικά φάρμακα μπαίνουν στην κλινική πράξη

Επιδημιολογία

Αυξανόμενη συχνότητα

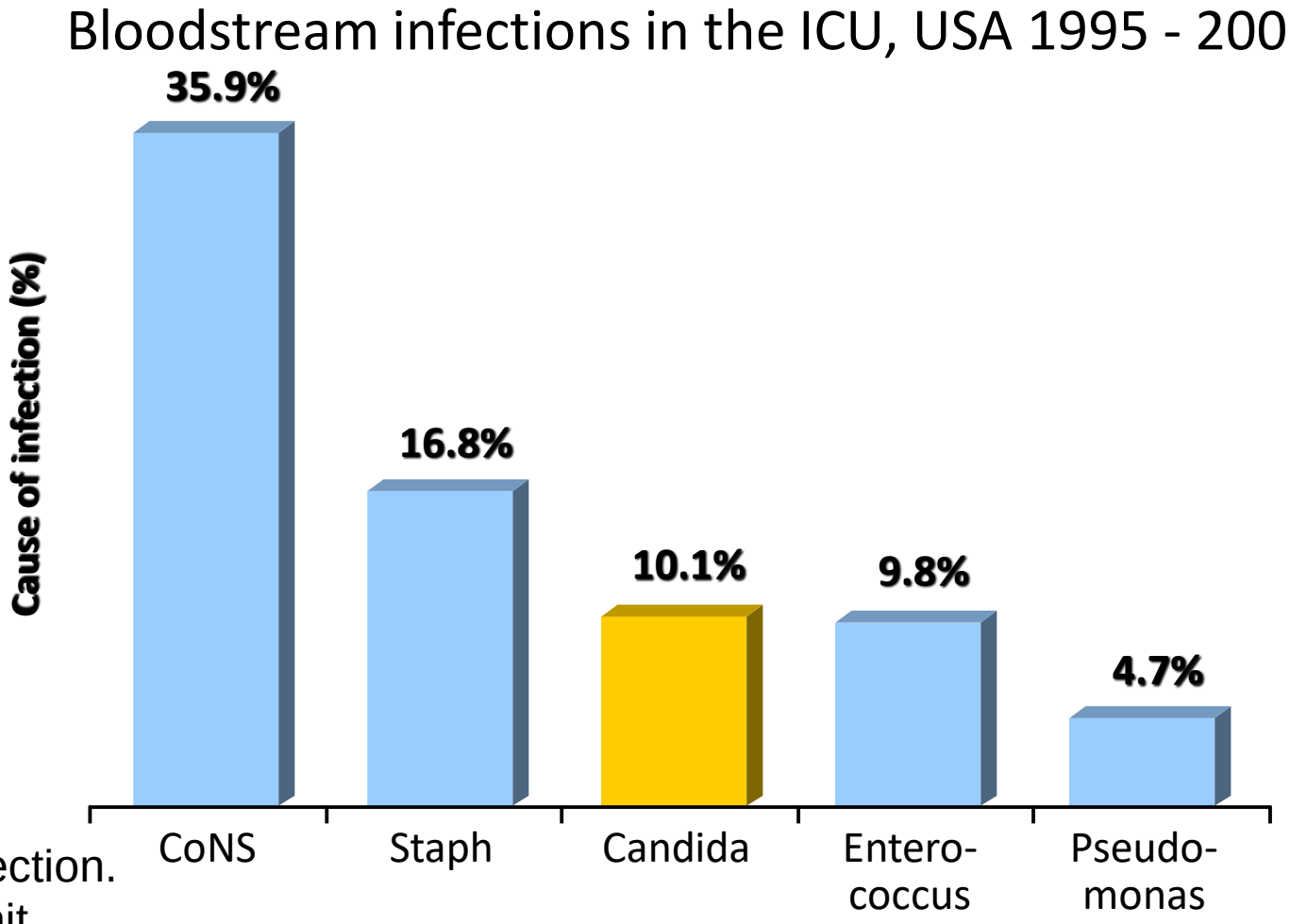
Μεγάλη θνησιμότητα

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



Bassetti M, . 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

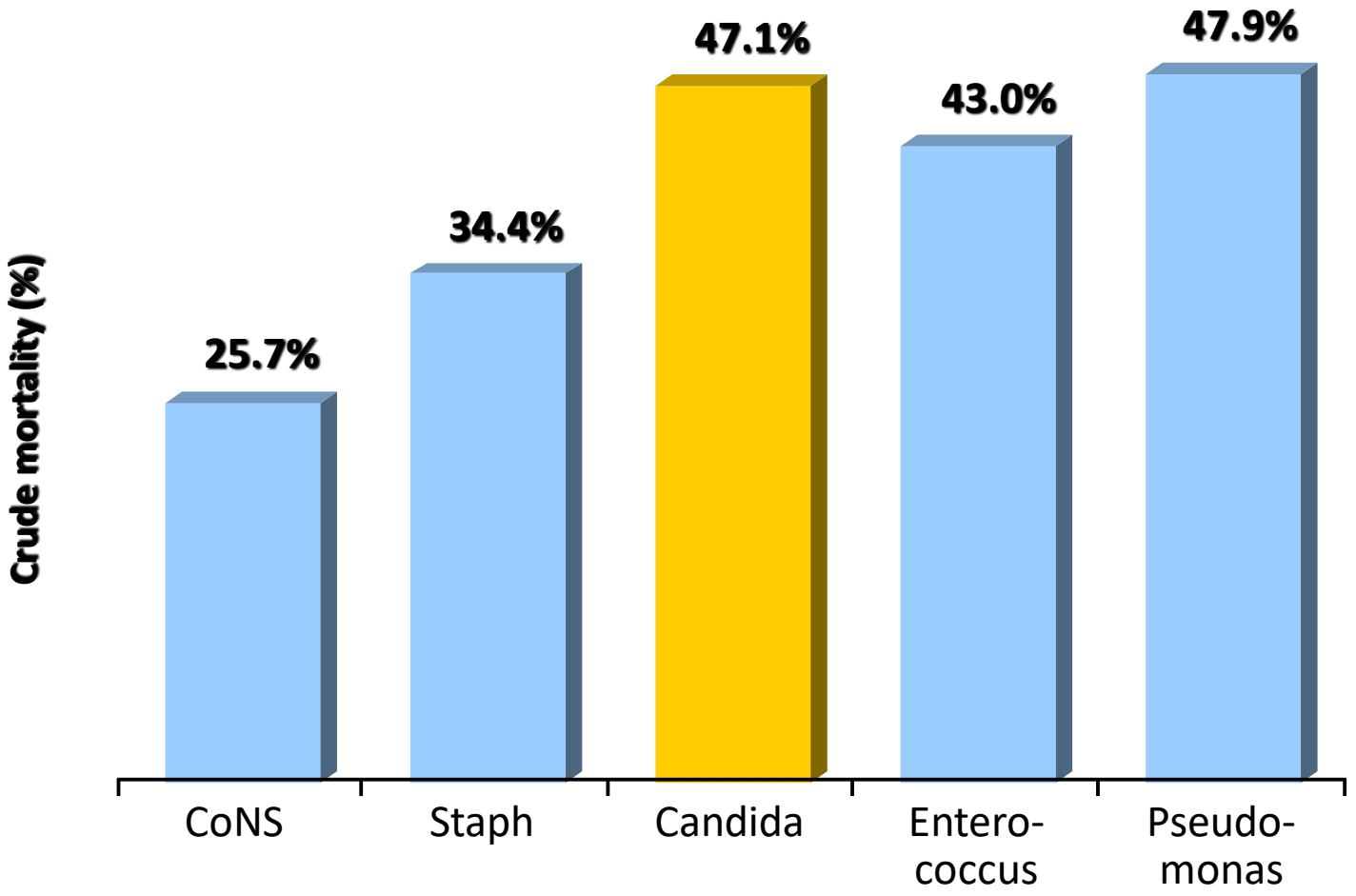
Parameter	No. of episodes	Mortality (%)	*p* value
Aetiological agent			
C. albicans	1,090	38.5	0.65
C. glabrata	269	45.0	0.02
C. parapsilosis	263	25.9	< 0.001
C. tropicalis	140	41.4	0.42
Underlying condition			
Surgery	892	35.3	0.26
Intensive care	791	42.4	0.02
Solid tumour	442	49.2	< 0.001
Haematological 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
≥ 70 years	556	47.7	< 0.001
Total population	1,942	37.9	

Tortorano AM, . 2004

IC is associated with high mortality in the ICU

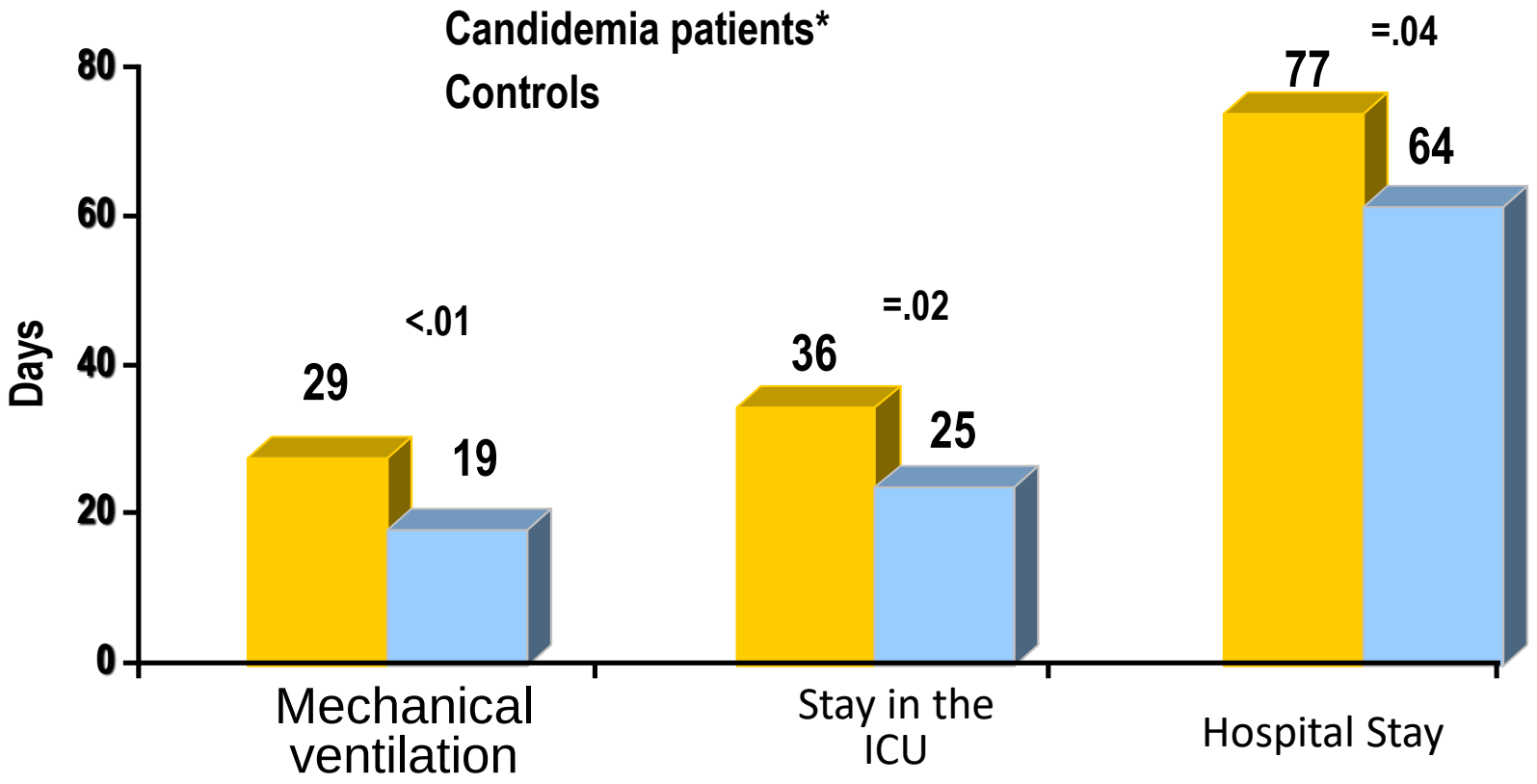
Crude mortality

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. . 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)

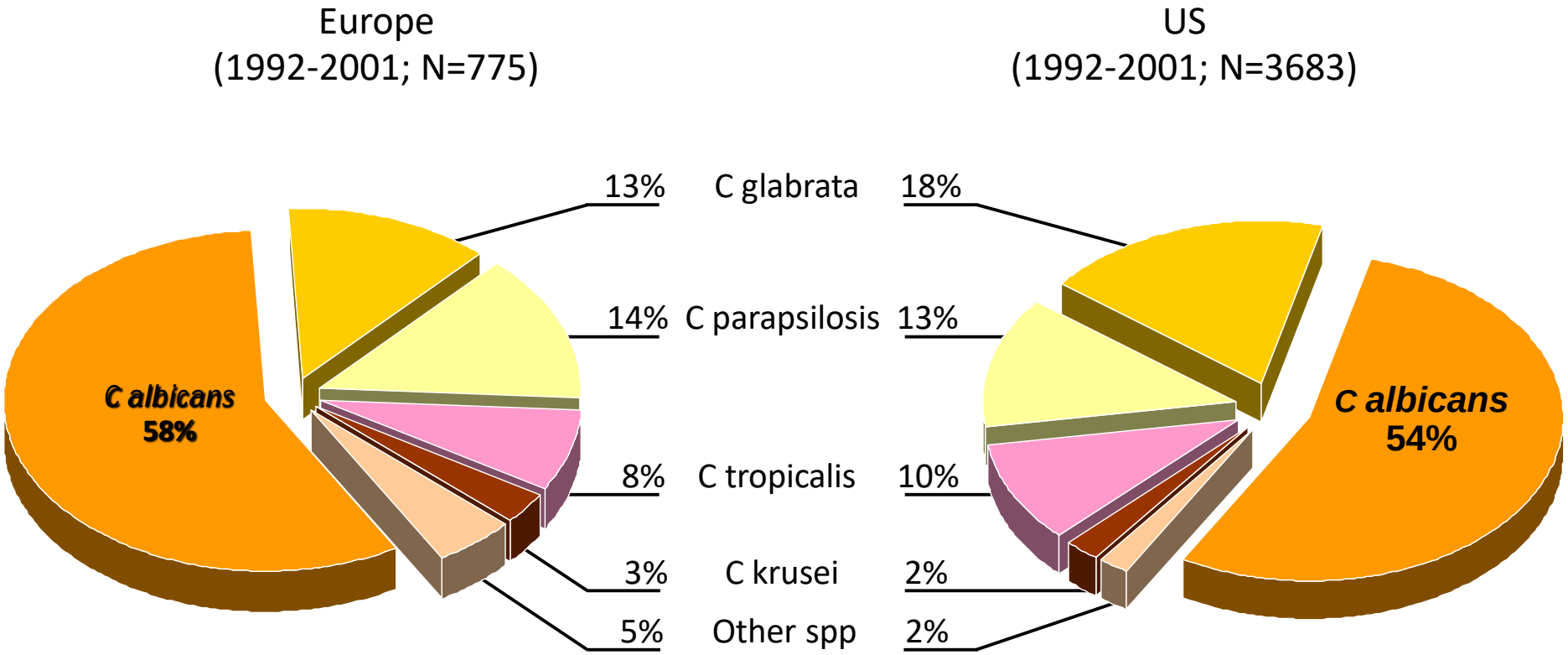
Source Adults: Nationwide Inpatient Sample 2000;

Clin Infec Dis 2005; 41:1232-9

Η επιδημιολογία μεταβάλλεται

Non-albicans Candida spp.

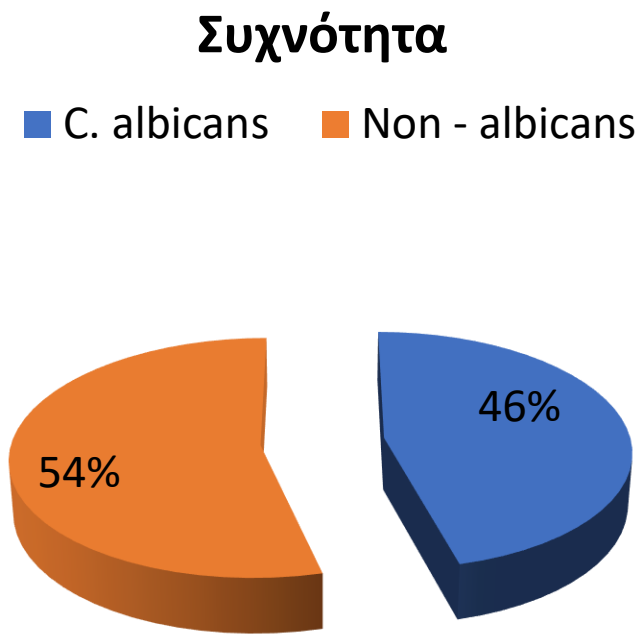
Κατανομή των *Candida* species το 2004



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



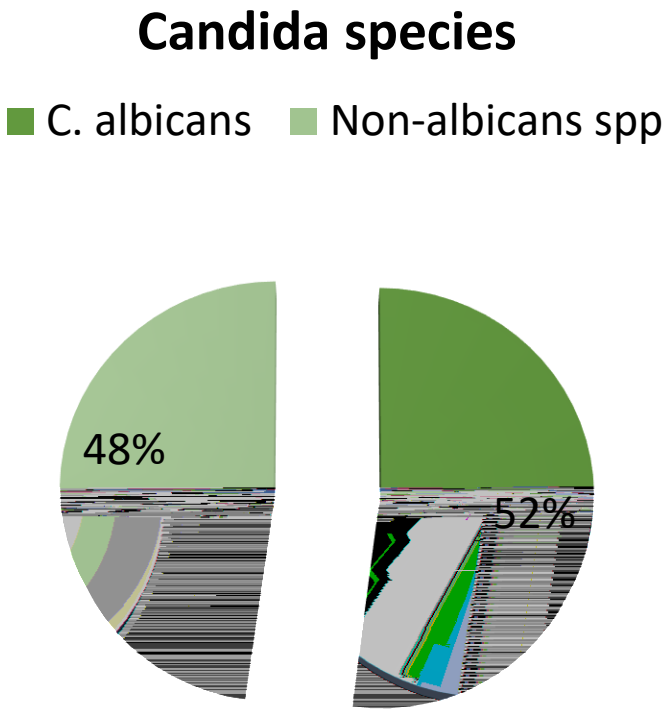
Horn DL, et al. Epidemiology and outcomes of candidemia in 2019 patients: data from the prospective antifungal therapy alliance registry. Clin Infect Dis. 2009;48:1695-703.

Ελληνική εμπειρία

Αιματολογικοί ασθενείς

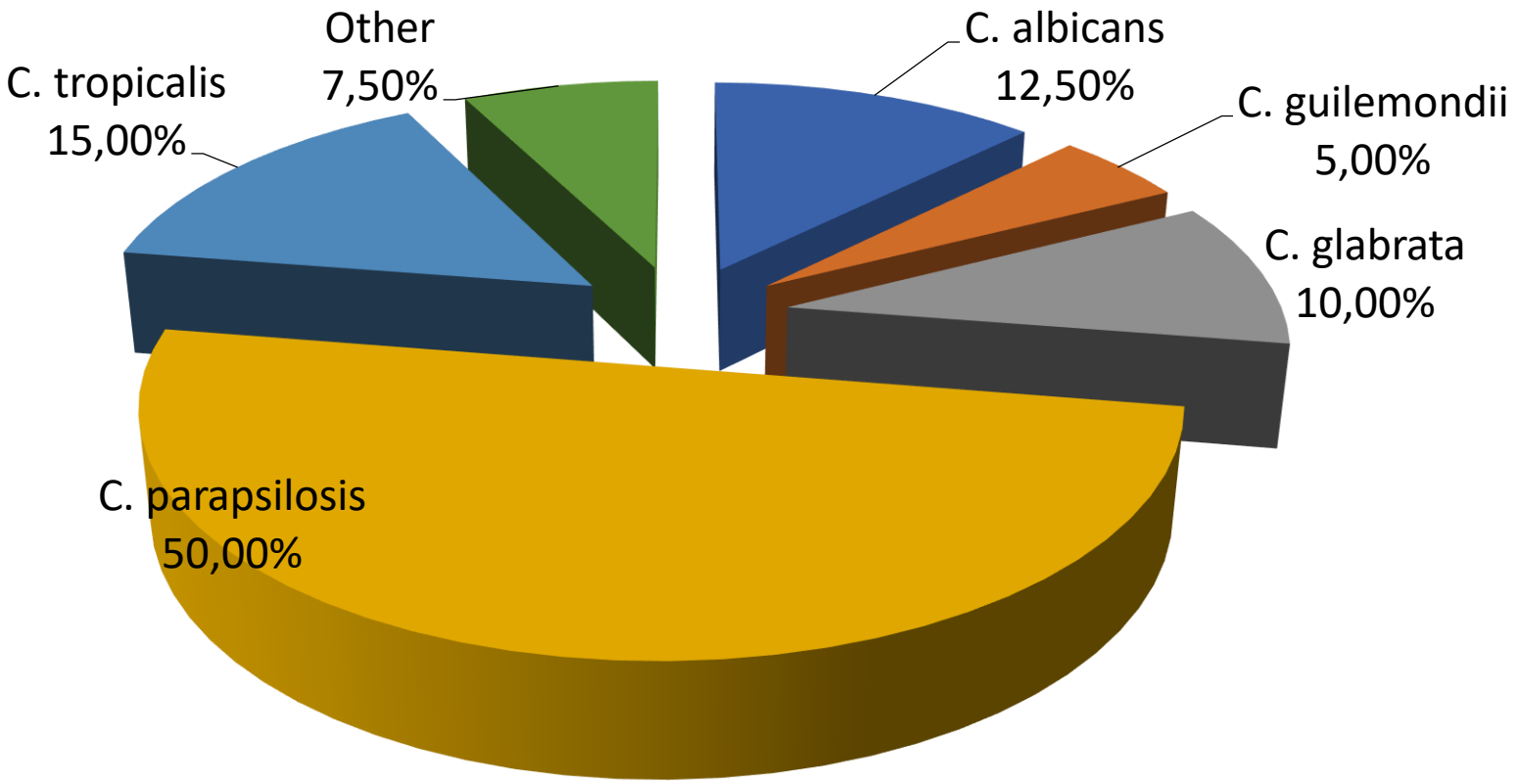
Ελληνική εμπειρία 2009-2011

- 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

Ελληνική εμπειρία σε αιματολογικούς ασθενείς 2009-2011



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

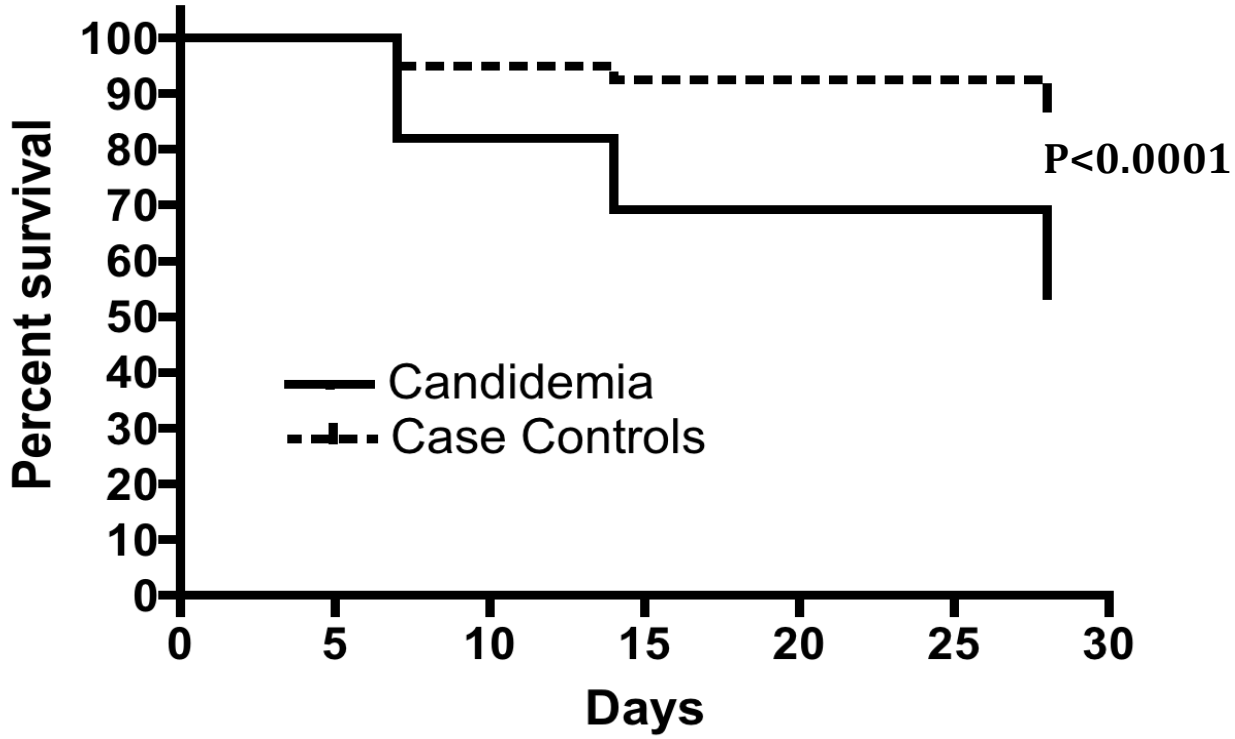
Gamaletsou M, et al. Clin Microb Infect 2014; 20: O50–O57

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	1.23 (0.92–0.91)	.13	…	

[redacted]

Chow JK et al. Factors Associated with Candidemia Caused by Non- Versus

Clinical Infectious Diseases 2008; 46:1206–13

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

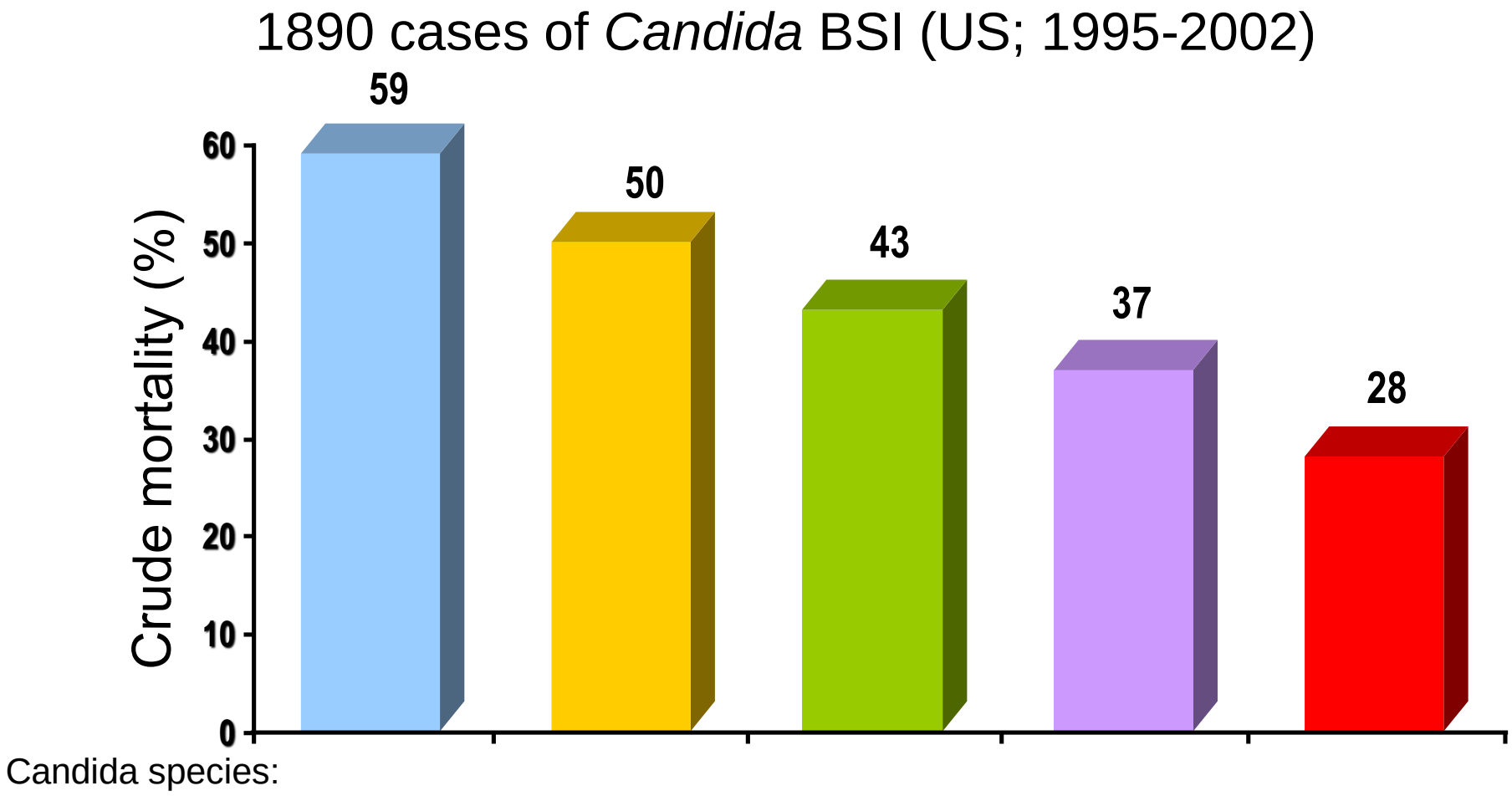
Species	Fluconazole MIC (µg/ml)			Percentage of isolates		
	50%	90%	Range	Susceptible	Susceptible–dose-dependent*	Resistant
	≤ 0.5	8	≤ 0.5 – >64	93.4	4.7	1.9
	≤ 0.5	≤ 0.5	≤ 0.5–16	99.7	0.3	0
	8	64	≤ 0.5 – >64	74.3	15.3	10.4
	1	4	≤ 0.5–32	96.6	3.4	0.0
	≤ 0.5	1	≤ 0.5–32	99.4	0.6	0.0
	32	64	8 – >64	3.5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

Messer SA, . 2006; **44:**1782–1787.

Τα non-albicans στελέχη

Μεγαλύτερη αντοχή μεγαλύτερη θνησιμότητα

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

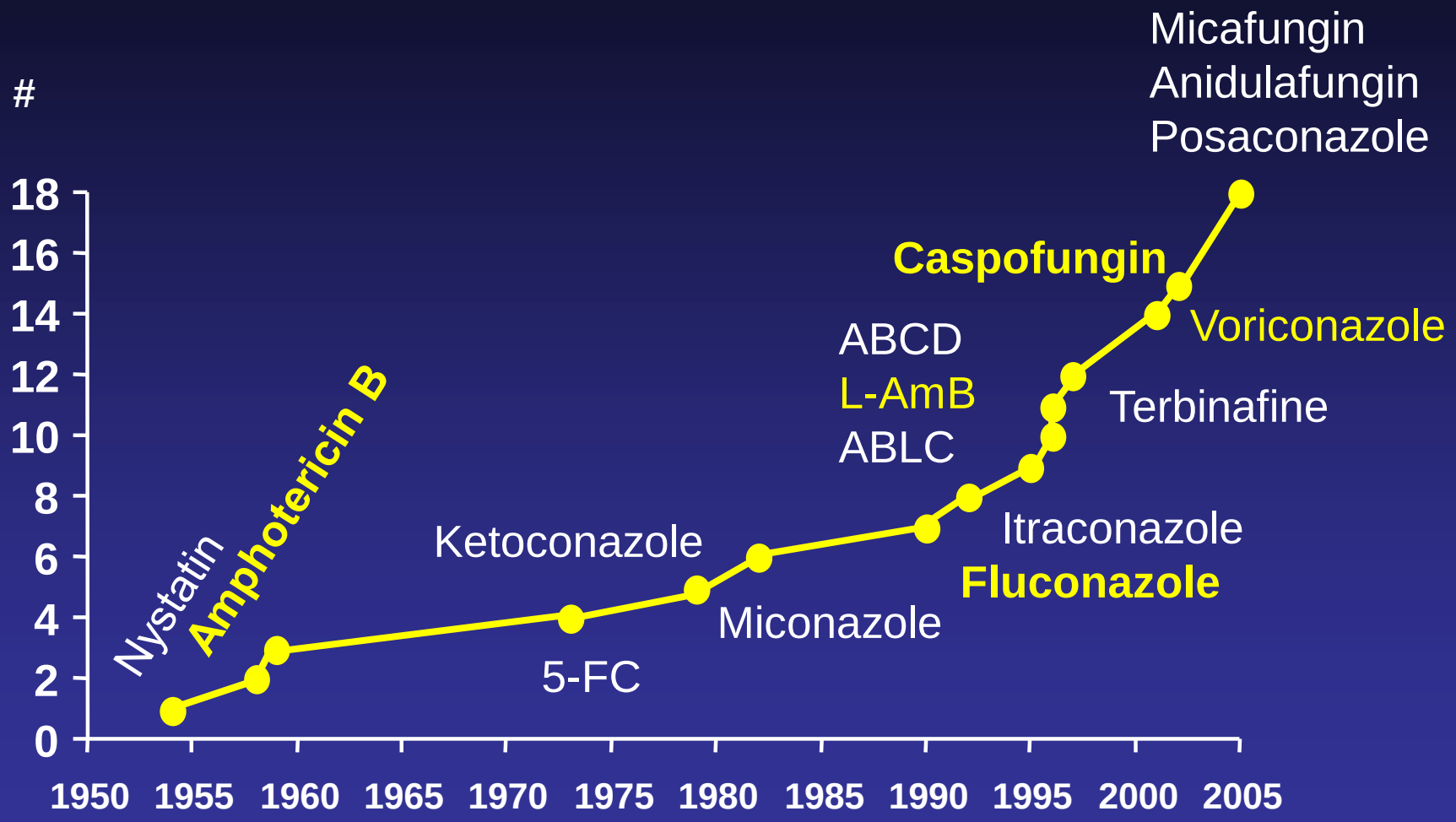


Adapted from Wisplinghoff H et al. Clin Infect Dis. 2004;39:309-317.

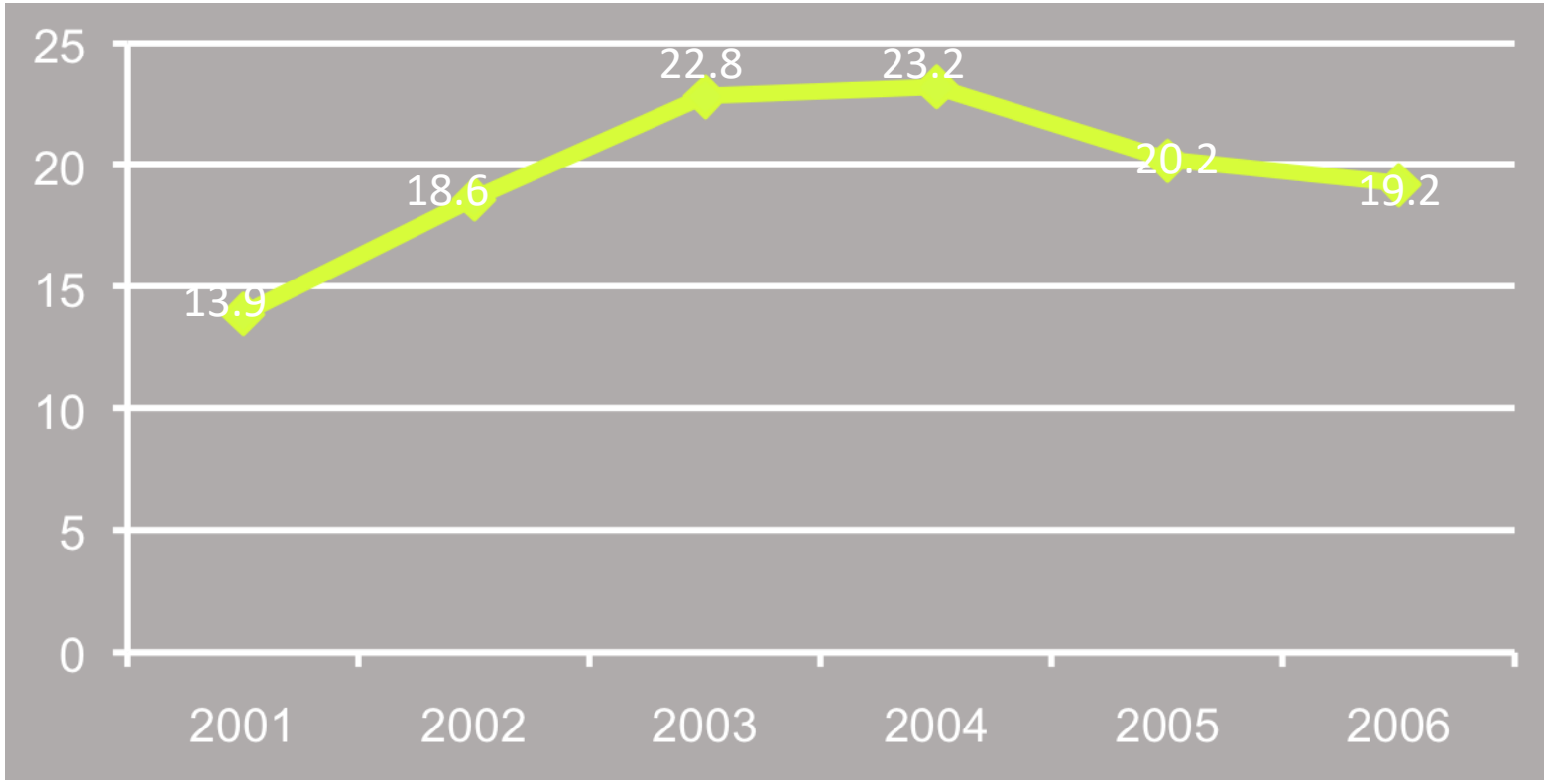
Νεώτερα αντιμυκητιασικά

Τι επίδραση είχε η εισαγωγή τους στην κλινική πράξη;

Επιτάχυνση στην ανακάλυψη



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%.

Παθοφυσιολογία

Ομάδες / παράγοντες κινδύνου

Ένας θαρραλέος γερμανός ειδικευόμενος χειρουργικής!

- **Μέχρι το 1960’s → η** *Candida* ʁ ʾ ʌ h ʿ ˉ ˇ < > ʁ ɹ ɦ < ʌ h ˉ ʁ ˊ ɦ ˋ ʁ ʿ h ˉ ˈ ˍ ˇ w ʌ ˍ ʁ ˊ ˇ ˋ ˍ ˇ
- **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*

(-)

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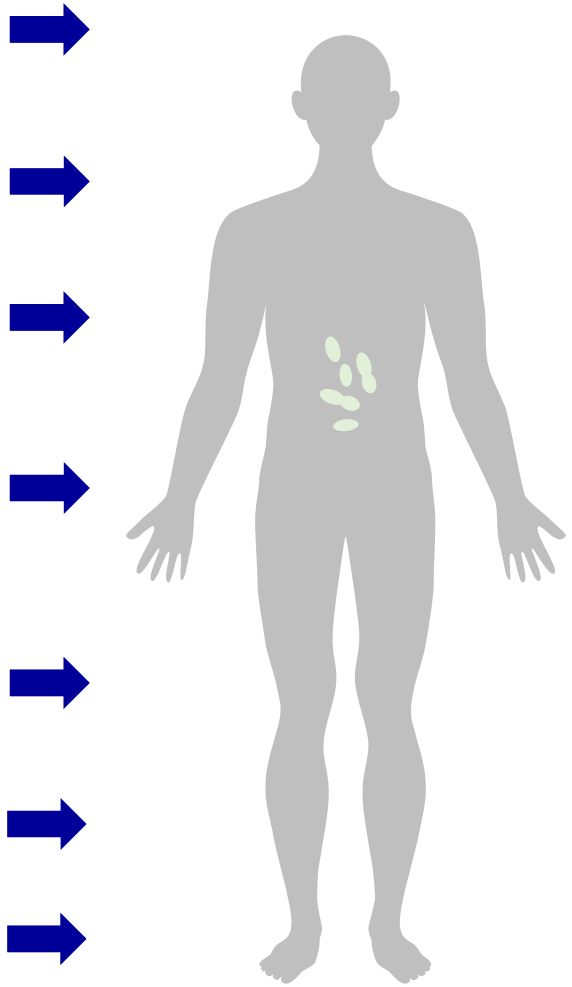


IV

Άμεση IV πρόσβαση
Μολυσμένο περιεχόμενο

/

,

-

•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

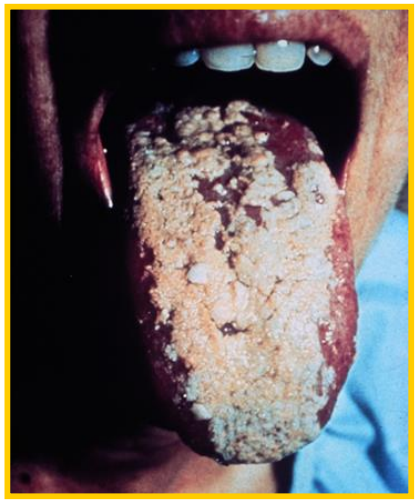
Sipsas NV, et al. Cancer 2009; 115:4745-52.

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.

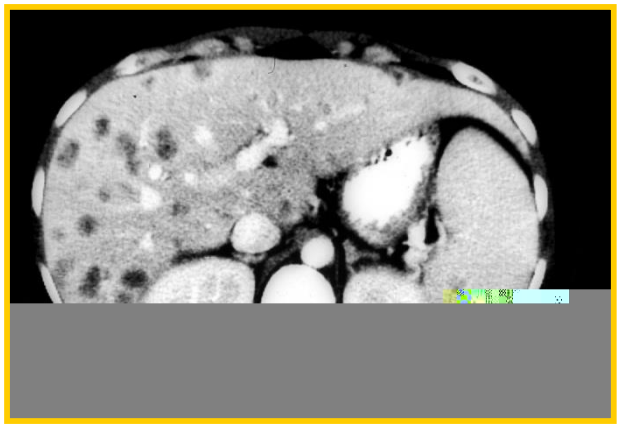
Pulmonary IC

- CT scan: multiple peripheral small nodules
- colonization in the airway is extremely common in ICU
- pneumonia is rare
- -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.

- Numerous small abscesses can

Διάγνωση

Καλλιέργεια αίματος

- Μόνο 35%-50% έχουν θετική καλλιέργεια κατά την έναρξη των συμπτωμάτων
- Η προφύλαξη μειώνει την ευαισθησία
- > 72 ώρες για θετικοποίηση για
- 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

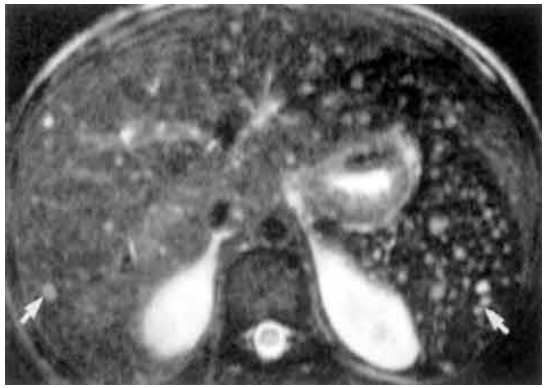
Karageorgopoulos DE, et al. Clin Infect Dis. 2011;52(6):750
Gupta P, et al. Mycoses 2017, 60, 2234–2240.
Lamoth F, Calandra T. J Antimicrob Chemother 2017, 72, i19–i28.
Wheat LJ. 2009; 30:367–77

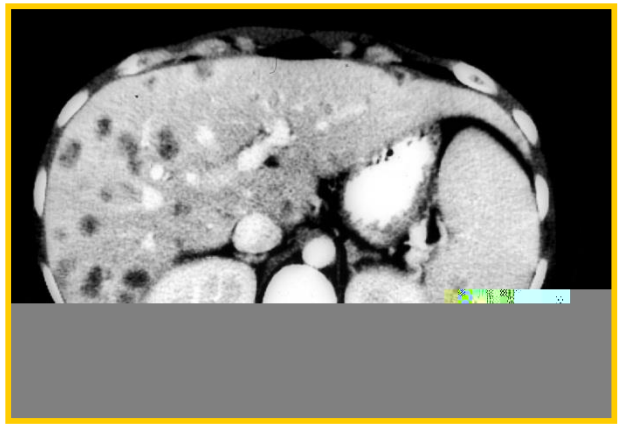
CT

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

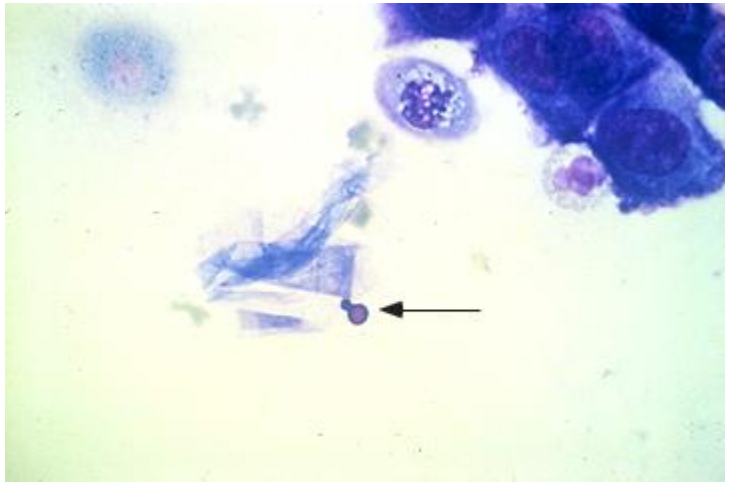
Radiologic Diagnosis in Hepatosplenic Candidiasis

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





Skin scraping in disseminated candidiasis



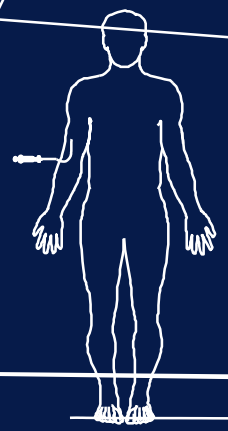
- A budding yeast (arrow) is visible in this Gram stain of a pustular skin lesion from a neutropenic patient.

Θεραπεία

Αρχές

‘Εγκαιρα

Pathogenesis of Invasive Candidiasis



Crude mortality
40%

No disease

Cultures/
antigen

Signs and
symptoms

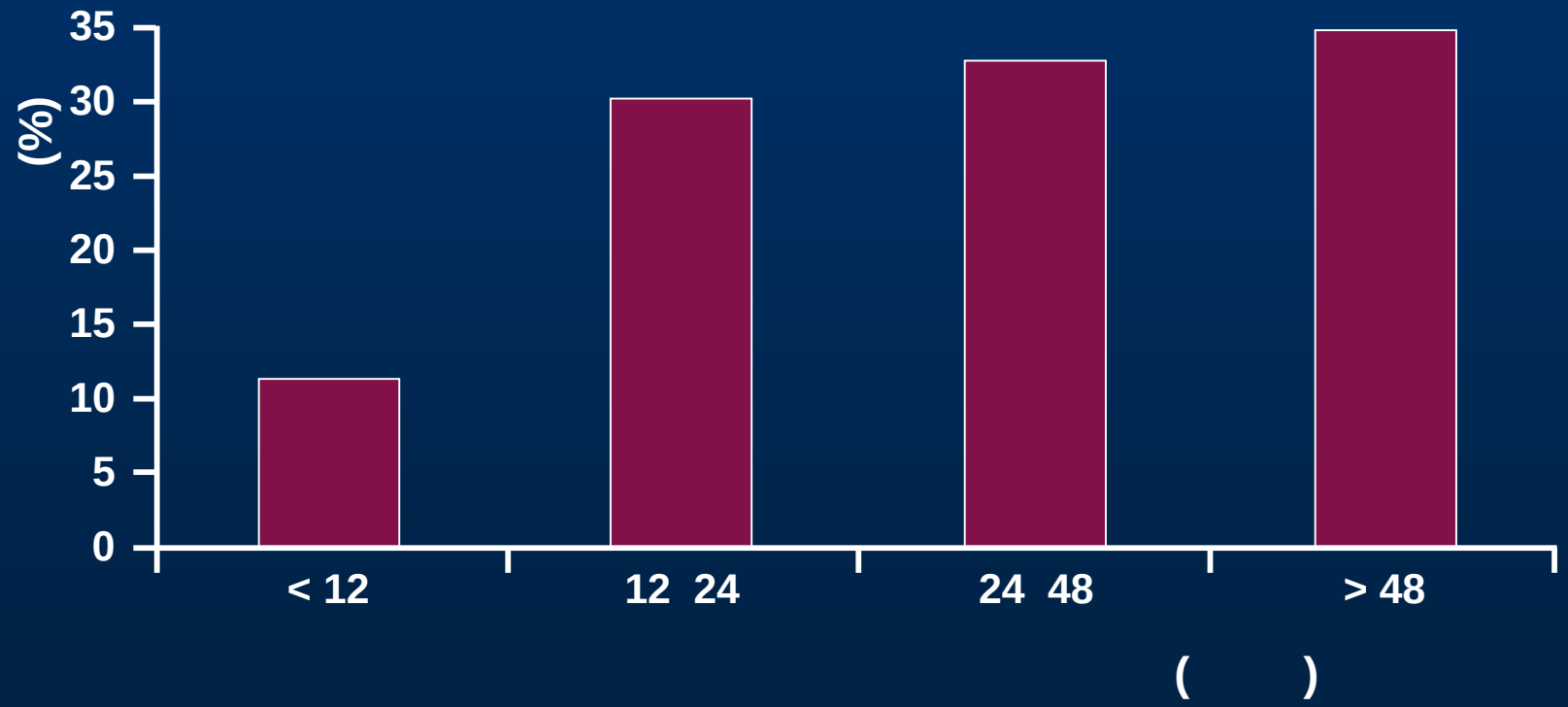
Cultures/
histopathology

Sequelae

Prophylaxis

Pre-emptive

Empiric



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

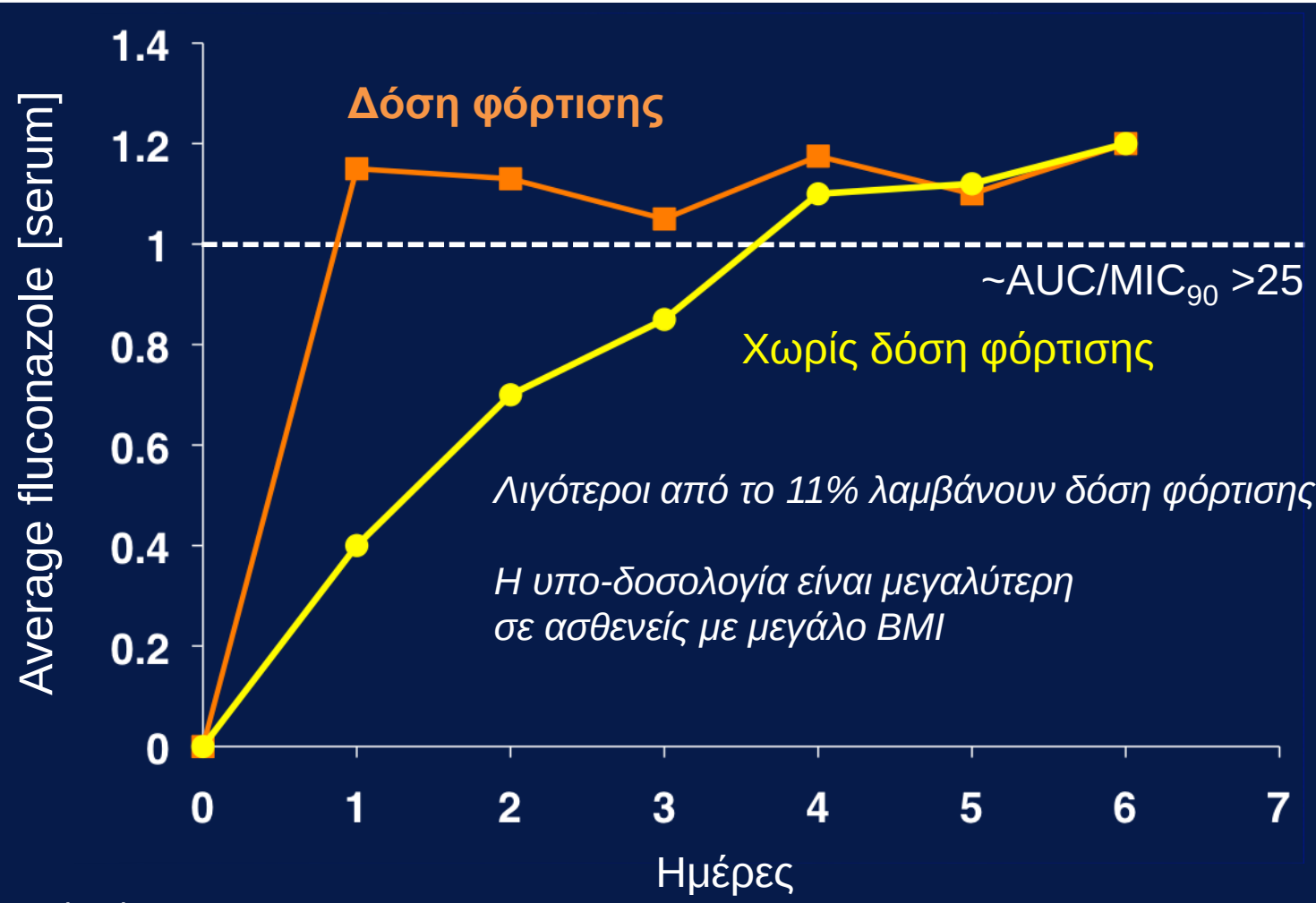
Ανάλογα με το είδος της Candida

Candida sp	AMB

Ανάλογα με το σημείο της λοίμωξης

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

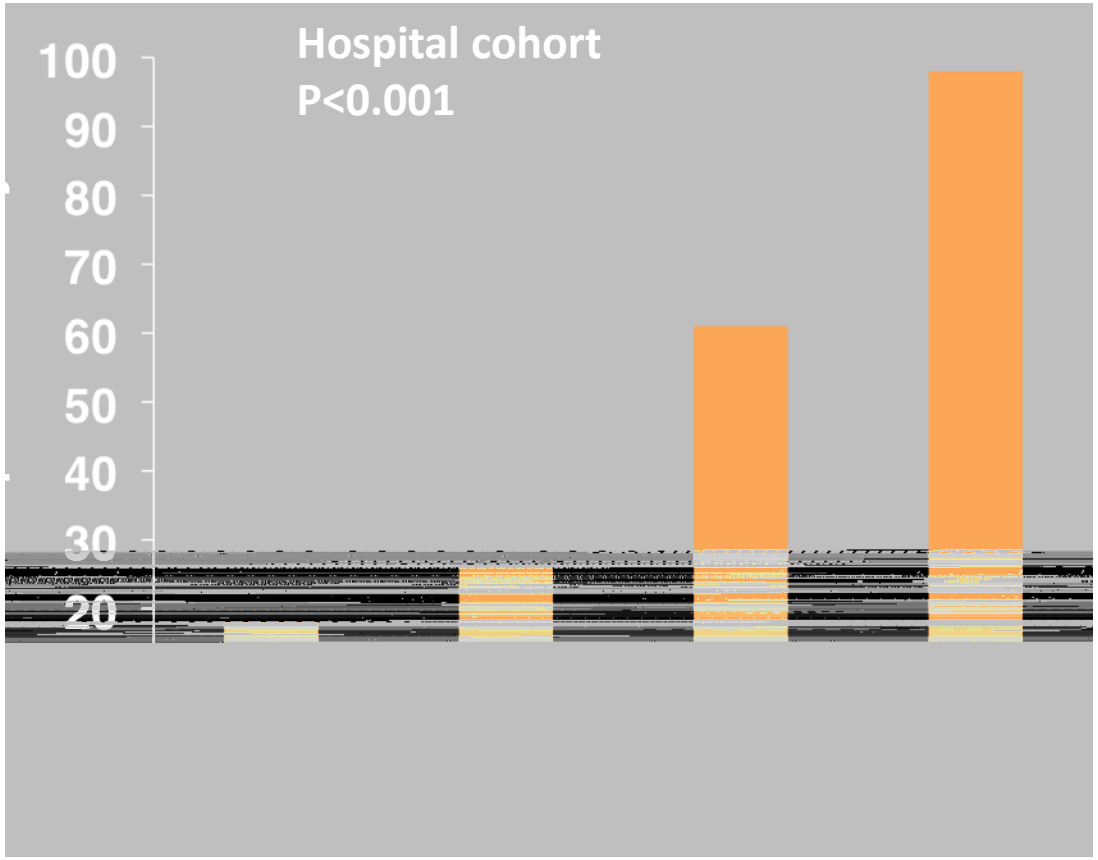
Risk factor	OR	95% CI	P value
Age	**1.01**	**1-1.02**	**0.02**
Apache II	**1.11**	**1.08-1.14**	**0.0001**
Immunosuppressive meds.	**1.69**	**1.08-2.44**	**0.01**
C. tropicalis	**1.64**	**1.10-2.44**	**0.01**
Removal of CVC	**0.49**	**0.34-0.70**	**0.0001**
Use of an echinocandin	**0.39**	**0.20-0.78**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



Risk factors

Early treatment strategies for IC

Prophylaxis

Empirical therapy

Targeted therapy

Χωρίς νόσο

Προφύλαξη

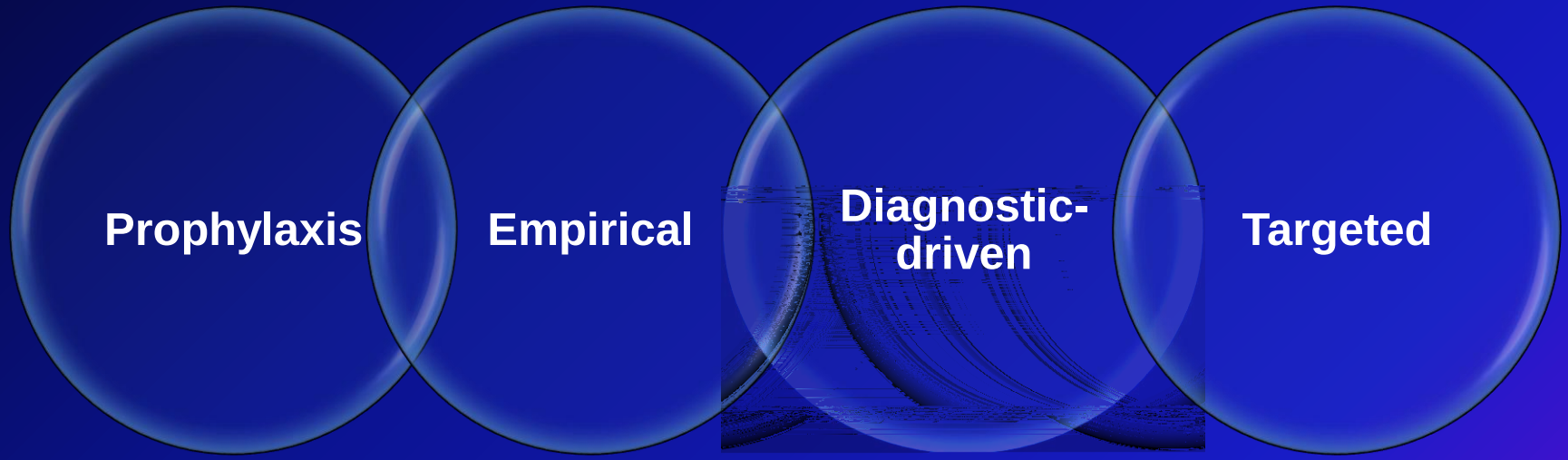
Ορολογικά / μοριακά

Σημεία και συμπτώματα

Καλλιέργειες / Ιστολογικές

Επιπλοκές

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**
- ***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 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.

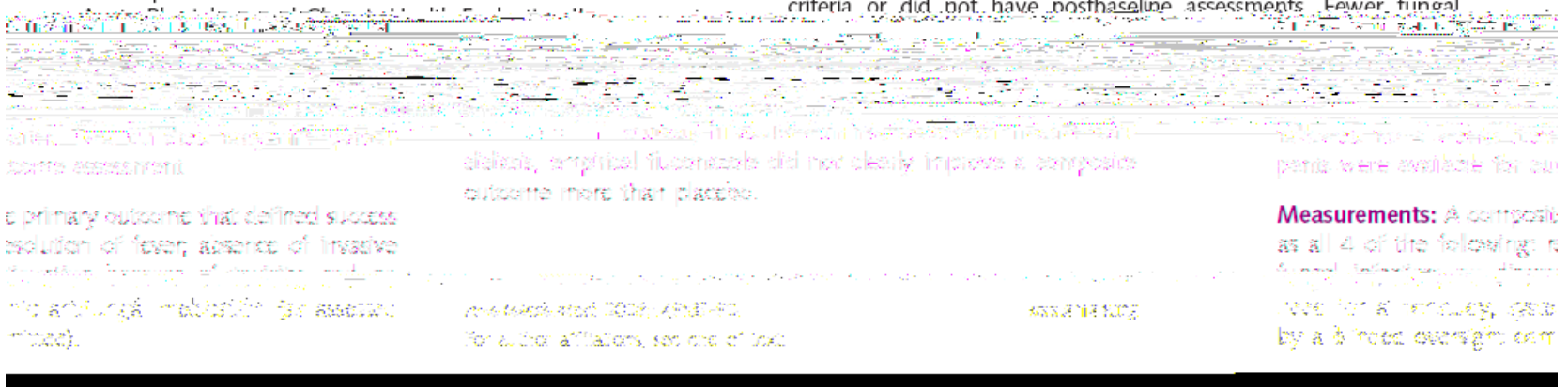
Design: Double-blind, placebo-controlled, randomized trial conducted from 1995 to 2000.

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

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 posthaseline assessments. Fewer fungal



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
  - .
- An alternative is to give an echinocandin
  - .
- Daily bathing of ICU patients with chlorhexidine, could be considered
  - .
- 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
  -

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

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 species
  -
- Lipid formulation AmB, 3–5 mg/kg daily, is an alternative if there is intolerance to other antifungal agents
  - (.
- Recommended duration of empiric therapy for suspected invasive candidiasis in those patients who improve is 2 weeks
  -

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
  - .
- 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 species
  -
- Voriconazole 400 mg offers little advantage over fluconazole as initial therapy
  -

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
  - .
- Recommended duration of therapy for candidemia without obvious metastatic complications is for 2 weeks
  - after documented clearance of species from the bloodstream
  - resolution of symptoms attributable to candidemia
  - .

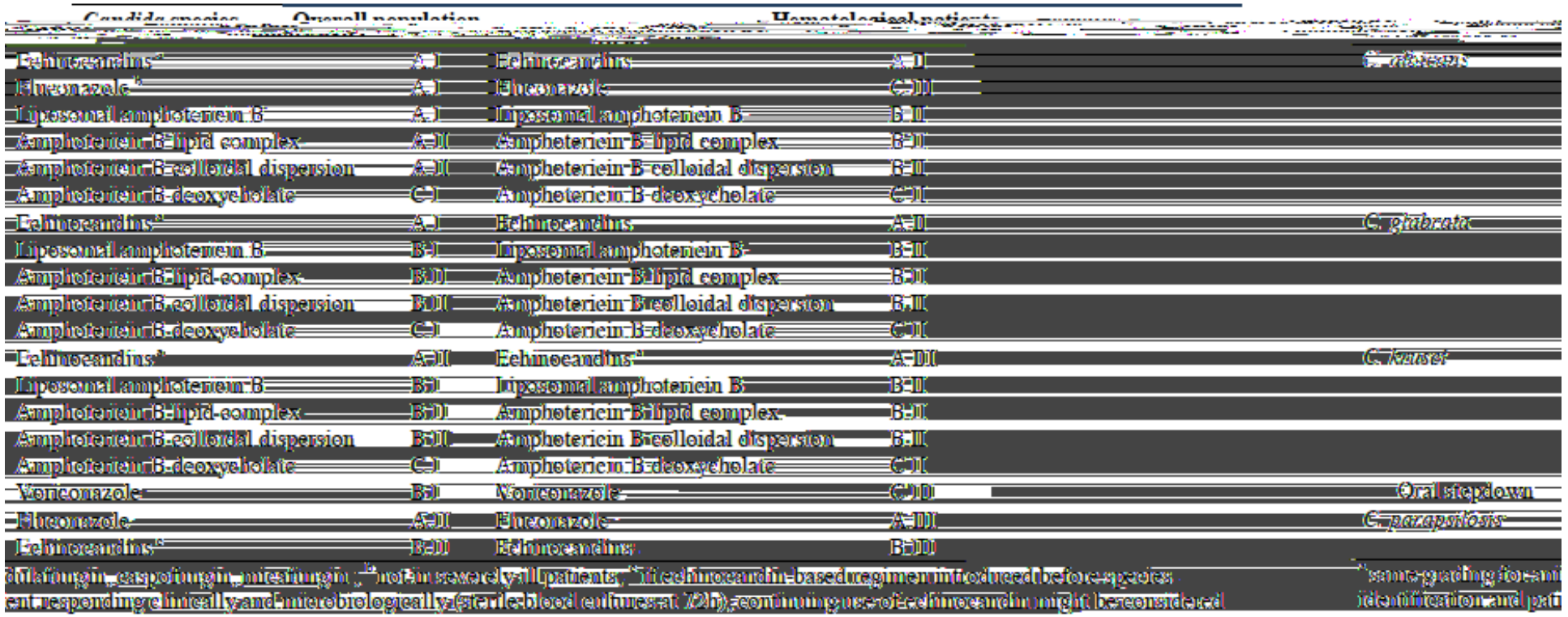
Papas PG et al. Clin Infect Dis 2016; 62(4):e1–50

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

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

Tissot F, et al. Hematologica 2017;

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



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 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

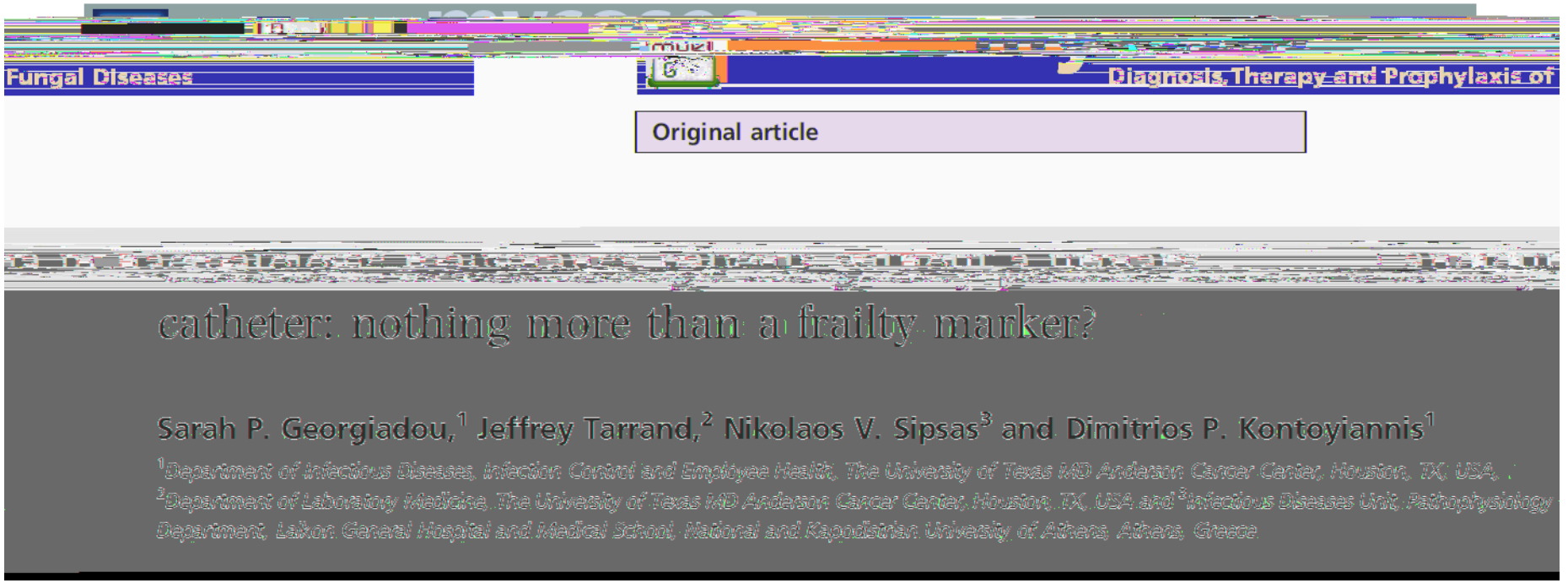
-

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

Κλινική σημασία καντιντουρίας



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

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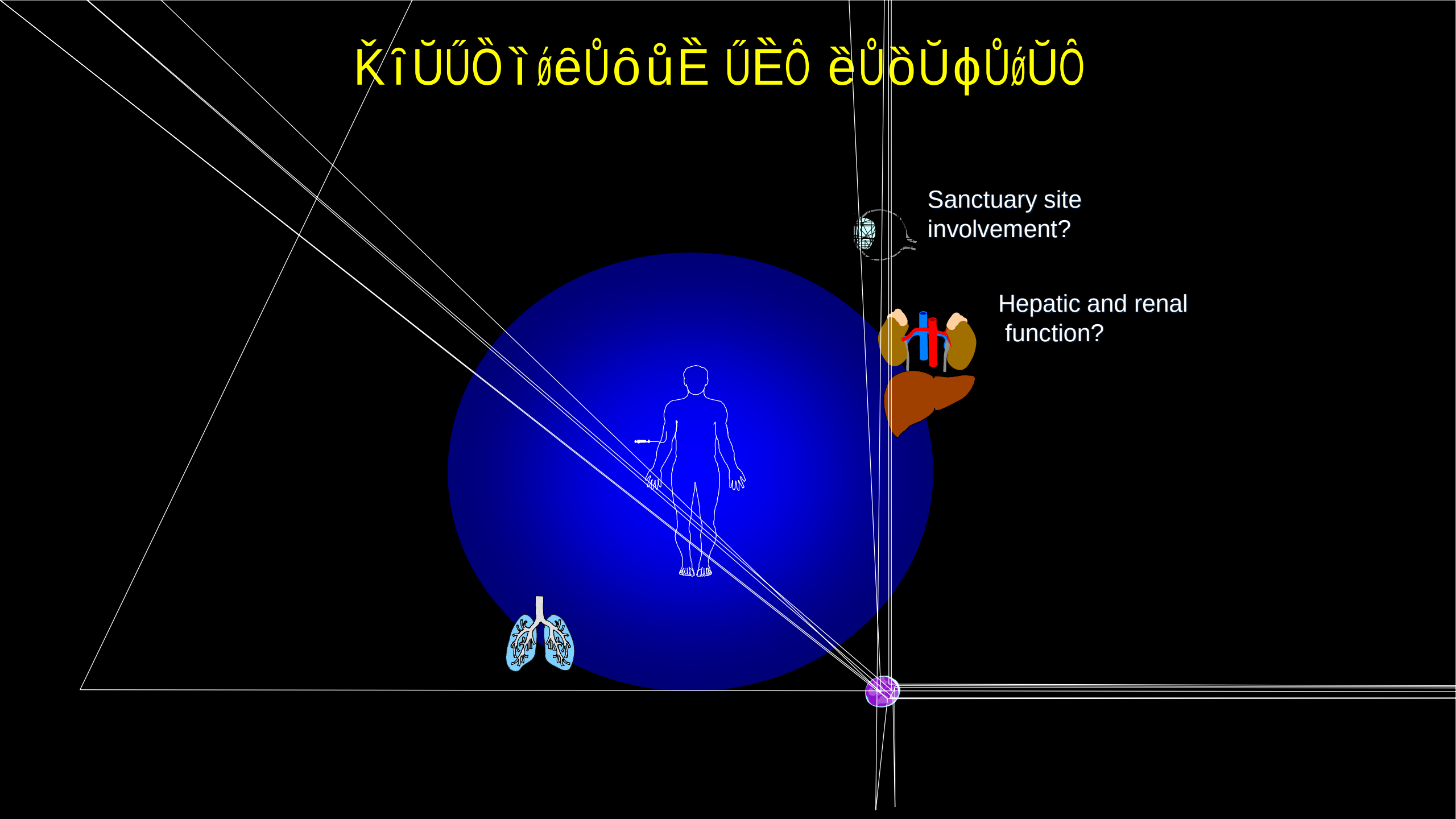
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