Invasive Candidiasis In The ICU Patients

22th Tunisian Congress of Infectious Diseases
2nd Arab Congress of Clinical Microbiology and Infectious Disease
By The Tunisian Society of Infectious Diseases (TSID)
& The Federation of Arab Societies for Clinical Microbiology and Infectious Diseases (FASCMID)

Hajjej Zied
May 2012

Definition

- Systemic, disseminated invasive, deep: confusion

- **Candidiasis "invasive"** :the presence of yeast in a sterile site.

- **Disseminated candidiasis** is characterized by the presence of yeast in at least two non contiguous organs or sterile sites

CID 2008

Definition

- **Candidemia: > 1 Hc positive**

- Candida in a **deep sterile site** (with or without + blood culture)
  - **endocarditis**
  - **Bone and joint infections**
  - **Infections CNS**
  - **Hepato-splenic candidiasis**

- **Endophthalmitis**

CID 2008

Definition

- Peritonitis: a localized invasive candidiasis
- Lung: almost = colonization
- Urine:
  - non invasive except renal abscess
  - Colonization of urinary catheter

CID 2008

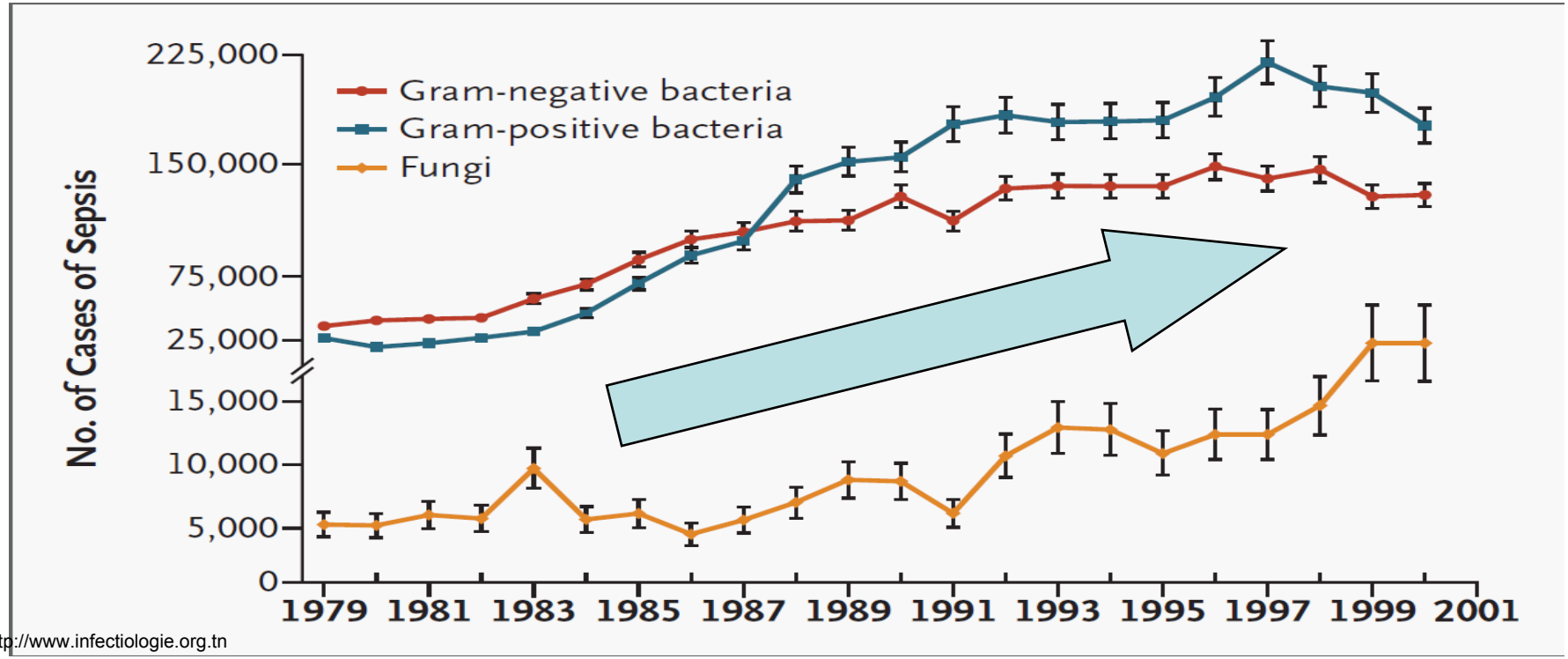
Epidemiology

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

The Epidemiology of Sepsis in the United States from 1979 through 2000

General trends



Epidemiology

- Invasive candidiasis: 70 to 90% of invasive fungal infections

Epidemiol infect 2001

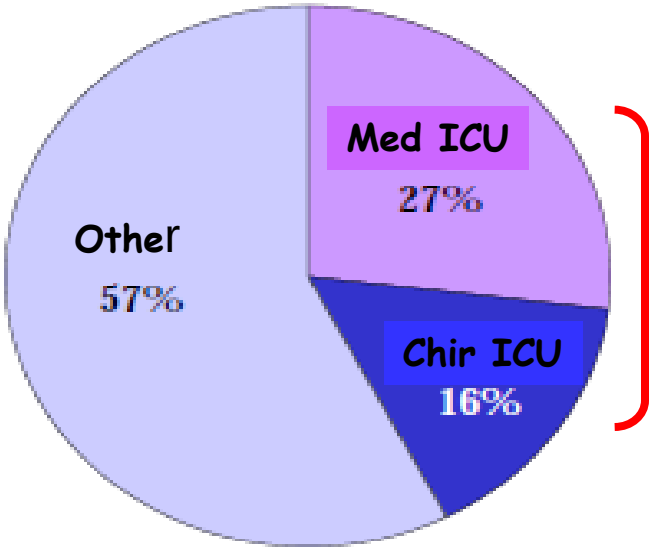
- Particularly described as infections of immunocompromised patients, they are now recognized as frequent infections of surgical or medical intensive care patients

Epidemiology

Results of the Observatory of yeasts:

- 27 laboratories in France
- 5 years of monitoring (2002-2007)
- 1824 episodes of fongemies
- 1726 initial episodes and 98 relapses.
- 62 episodes of co-infections (2 or 3 species)
- 1776 individuals concerned
- 1680 adults (59% ♂), mean age = 59 -17 years

33%	Onco hematology
10.5%	digestive surgery
9%	Gastroenterology
7%	Infectious desease
4%	Emergency
3%	pneumonology



Epidemiology

- Incidence of candidemia :
  0.5-3 episodes/1000 hospitaliz stable
  for 10 years.

Crit Care, 2008

- ICU: **2-12 /1 missions** developed
  candidem

Int Care Med 2003

. **Re ed mortality** : 38% (5 à 71%)

Eur J Clin Microbiol Infect Dis, 2006

Pathogens well installed

Epidemiology

	Tortorano et al., 2006 [1] (n=569) (%)	Trick et al., 2002 [46] (n=2759) (%)	Diekema et al., 2002 [47] (n=254) (%)	Richet et al., 2002 [13] (n=377) (%)	Pfaller et al., 2001 [12] (n=1184) (%)	Marchetti et al., 2004 [48] (n=1137) (%)	Leroy et al., 2009 [18] (n=71)[a] (%)
C. albicans	58,5	59	58	53	55	66	57
C. glabrata	13	12	20	11	15	15	17
C. parapsilosis	15	11	7	16	15	1	7,5
C. tropicalis	6	10	11	9	9	9	5
C. krusei	1	1	2	4	1	2	5
Autres	7	7	2	6	1	7	8,5

Increased rate of non albicans

ICU

J of Inter Med 2011

Case report

Ms. B.D, 63 years old admitted in ICU for severe sepsis starting at day 15 post operative of gastrectomy
(for stromal tumor of the greater tuberosity)
complicated by fistula for which it was taken at day 6 postoperative.

Ms B.D……/Past history

- Obesity (160 cm-100 kg)
- Insulin-requiring Diabetes

- Hypertension
- Dyslipidemia

- Coronary artery disease
- Treatement: Insulin, calcuim blocker,Statin,

Ms B.D...../H0

- fever.
- Tachycardia at 120 bpm.
- Hypotension: 78/34 mmHg.

- VCC: parenteral nutrition.
- Urinary catheter.

- Ongoing treatement: Tazocillin / metronidazol.

- C. albicans in oral and stool samples.

Ms B.D……/H2

Should we start antifungal treatment ??

Major factors

Colonization by Candida yeasts

Prior or concomitant antibiotic therapy

Humoral or cellular immunosuppression

neutropenia

Extensive burns (> 50%)

gastrointestinal perforation

Major abdominal surgery

Alterations in transit (ileus or diarrhea)

parenteral nutrition

hemodialysis

Minor factorss *

Age (newborns and the elderly)

Comorbidity (diabetes /renal failure)

Surgery

urinary catheter

Multiple intravascular access

Prolonged stay in the ICU> 7 days

Candiduria> 105 cfu / ml

C. tropicalis	• Neutropenia and bone marrow transplantation
C. krusei	• Fluconazole use • Neutropenia and bone marrow transplantation
C. glabrata	• Fluconazole use • Surgery • Vascular catheters • Cancer • Older age
C. parapsilosis	• Parenteral nutrition and hyperalimentation • Vascular catheters • Being neonate [2] *

J .Hosp. Infect 2002
CID 2001

ICU: 650 pts
29 colonized , 11 infected (CI>0,5)

Pittet and al .Ann surg 1994

Colonization Parameters	Sensitivity	Specificity	Positive Predictive Value†	Negative Predictive Value
No. of distinct body sites colonized with *Candida spp*				
Two sites or more	100	22	44	100
More than two sites	73	56	50	77
Three sites or more	45	72	50	68
Candida colonization index	100	69	66	100

Heads or Tails ???

Do not treat patients with risk factors if CI <0.5???

A bedside scoring system ("Candida score") for early antifungal treatment in nonneutropenic critically ill patients with *Candida* colonization*

Crit Care Med 2006 Vol. 34, No. 3

Variable	Coefficient (β)	Standard Error	Wald χ^2	*p* Value
Multifocal *Candida* species colonization	1.112	.379	8.625	.003
Surgery on ICU admission	.997	.319	9.761	.002
Severe sepsis	2.038	.314	42.014	.000
Total parenteral nutrition	.908	.389	5.451	.020
Constant	−4.916	.485	102.732	.000

ICU, intensive care unit.

Candida score = .908 × (total parenteral nutrition) + .997 × (surgery) + 1.112 (multifocal *Candida* species colonization) + 2.038 (severe sepsis). Candida score (rounded) = 1 × (total parenteral nutrition) + 1 × (surgery) + 1 (multifocal *Candida* species colonization) + 2 × (severe sepsis). All variables coded as follows: absent, 0; present, 1.

Usefulness of the "*Candida* score" for discriminating between *Candida* colonization and invasive candidiasis in non-neutropenic critically ill patients: A prospective multicenter study

Crit Care Med 2009 Vol. 37, No. 5

Cutoff Value	Incidence Rate (%) (95% CI)	Relative Risk (95% CI)
<3	2.3 (1.1–3.5)	1
3	8.5 (4.2–12.7)	3.7 (1.8–7.7)
4	16.8 (9.7–23.9)	7.3 (3.7–14.5)
5	23.6 (12.4–34.9)	10.3 (5.0–21.0)

Do better :Sensitivity : 81 % et Specificity : 74 %

Can yeast isolation in peritoneal fluid be predicted in intensive care unit patients with peritonitis?*

Hervé Dupont, MD; Agnes Bourichon; Catherine Paugam-Burtz; Jean Mantz; Jean-Marie Desmonts

Grade of Score	Se	Sp	PPV	NPV	OA
Grade A	3	100	40	100	40
Grade B	33	87	46	79	54
Grade C	84	50	67	72	71
Grade D	100	13	100	64	65

Crit Care Med 2003 Vol. 31, No. 3

Case report

which molecule used?

Guidelines

- **USA**
  - *Aspergillus* IDSA 2008
  - *Candida* IDSA CID 2009
- **France**
  - SFAR/SPILF/SRLF 2004
  - Affsaps 2008
- **Europe:**
  - ECIL: leucémies 2009
  - ESCMID: candida 2011

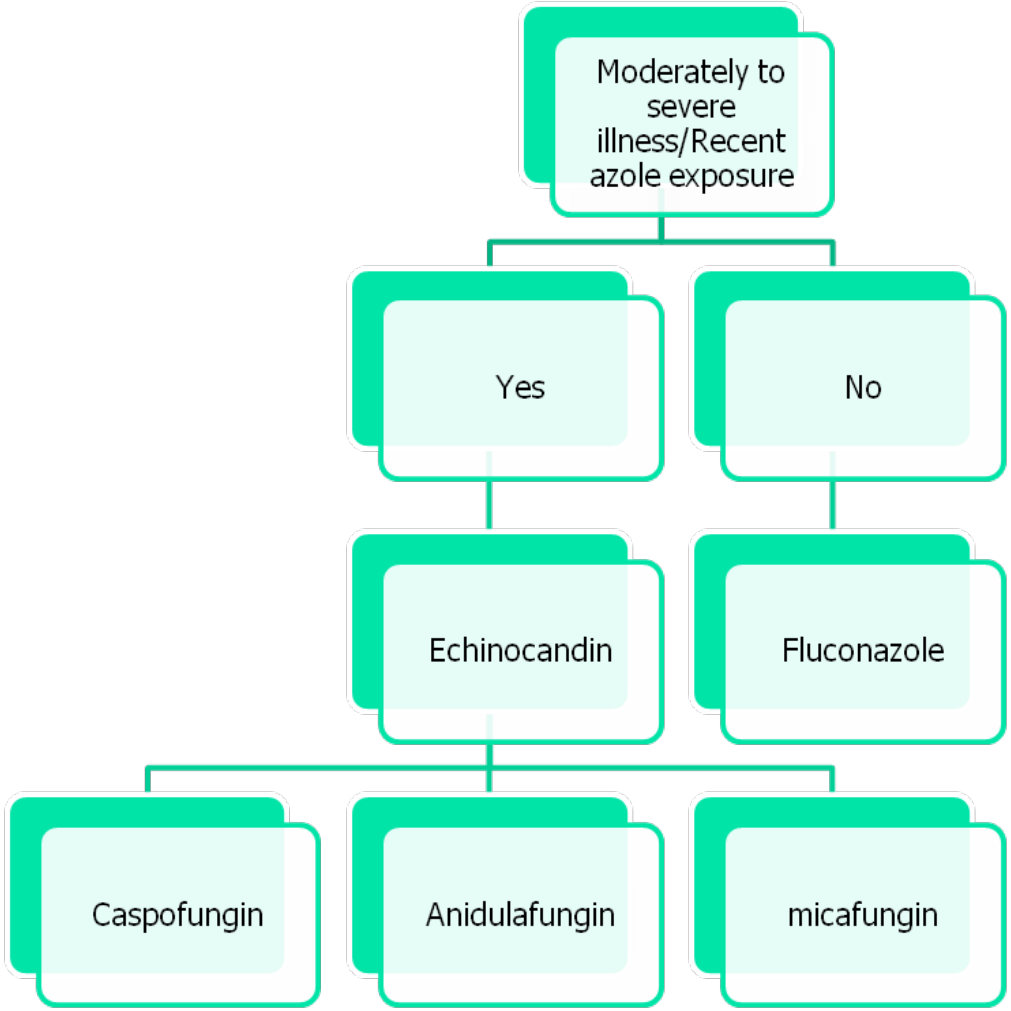
ESCMID Diagnostic & Management Guideline for Candida Diseases 2011

Clinical Practice Guidelines for the Management of Candidiasis: 2009 Update by the Infectious Diseases Society of America

Peter G. Pappas,[1] Carol A. Kauffman,[2] David Andes,[3] Daniel K. Benjamin, Jr.,[4] Thierry F. Calandra,[5] John E. Edwards, Jr.,[6] Scott G. Filler,[7] John F. Fisher,[8] Bart-Jan Kullberg,[9] Luis Ostrosky-Zeichner,[10] Annette C. Reboli,[11] John H. Rex,[12] Thomas J. Walsh,[13] and Jack D. Sobel[14]

- **IDSA 2009**
  - Indication:risk factors, markers, colonization **B3**
  - Same invasive candidiasis **B3**
- **ESCMID 2011**
  - Risk patients, and fever of unknown origin: **C3**
  - Adults with fever despite ATB: **D1**

Treatment Guidelines for Candidiasis • CID 2009:



800 mg [12mg/kg],
then 400 mg [6 mg/kg] daily

70 mg
then 50 mg daily

200 mg
then 100 mg daily

100 mg daily

la SFAR, la SPILF et la SRLF

Creatinine <1.5 normal

NON-neutropenic
Anterior Tt. azole?

Yes

Amphotericin:
1 mg/kg daily

No

Amphotericin : 1 mg/kg daily
Or
Fluconazole : 800-mg then 400 mg

Creatinine >1.5 normal

NON-neutropenic
Anterior Tt. azole?

No

Fluconazole: 800-mg
then 400 mg

Yes

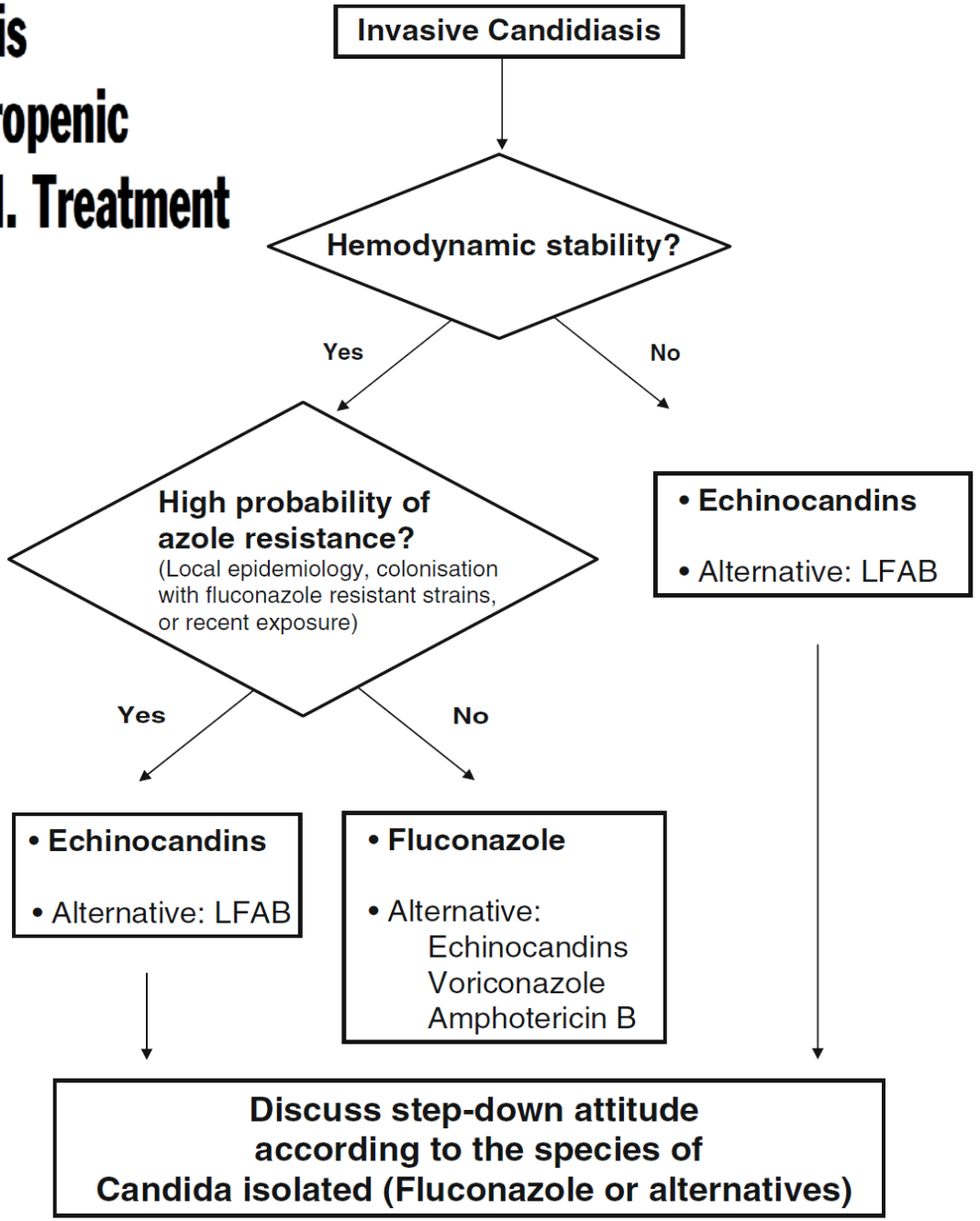
Caspofungin loading dose of 70 mg,then 50 mg daily
Or
lipid formulation of amphotericin B 3 mg/kg daily

2004

Management of invasive candidiasis and candidemia in adult non-neutropenic intensive care unit patients: Part II. Treatment

Benoît P. Guery
Maiken C. Arendrup
Georg Auzinger
Élie Azoulay
Márcio Borges Sá
Elizabeth M. Johnson
Eckhard Müller
Christian Putensen
Coleman Rotstein
Gabriele Sganga
Mario Venditti
Rafael Zaragoza Crespo
Bart Jan Kullberg

Intensive Care Med (2009) 35:206–214
DOI 10.1007/s00134-008-1339-6



Case report

Fluconazole : 800-mg then 400 mg

Ms B.D...../J4

- **Colistin/ Tigecyclin/Keep Fluconazole stop vancomycin**
- Thoraco abdominal CT
- Fundoscopy
- TOE

} metastatic complications

- Intravenous catheter removal is strongly recommended for nonneutropenic patients with candidemia (A-II).

Before identification

	ESCMID	IDSA
echinocandin	A1	A1 (severe and recent azole exposure): A3
L-Amb	B1	If intolerance
Autre AmB-L	C2	No
AmB-D	D1	A1
Fluconazole	C1	A1 (less critically ill and who had no recent azole exposure): A3
Voriconazole	B1	No
Itraconazole *	D2	

* Out of MAH

IDSA: CID 2009
ECCMID2011

Ms B.D...../J8

Switch Caspofungin 70 mg daily

After identification

IDSA 2009

C. albicans: Transition to fluconazole **A2**
C. glabrata: echinocandin: **B3**
If initial treatement with azole is effective : continue : **B3**
C. parapsilosis: fluconazole ou AmB-L: **B3**
C. kruzei: echinocandin ou AmB-L ou voriconazole: **B3**

ESCMID 2011

PO relay at day 10 if susceptible species and stable patient : **A2**

Ms B.D...../J12

7. Recommended duration of therapy for candidemia without obvious metastatic complications is for 2 weeks after documented clearance of *Candida* species from the bloodstream and resolution of symptoms attributable to candidemia (A-III).

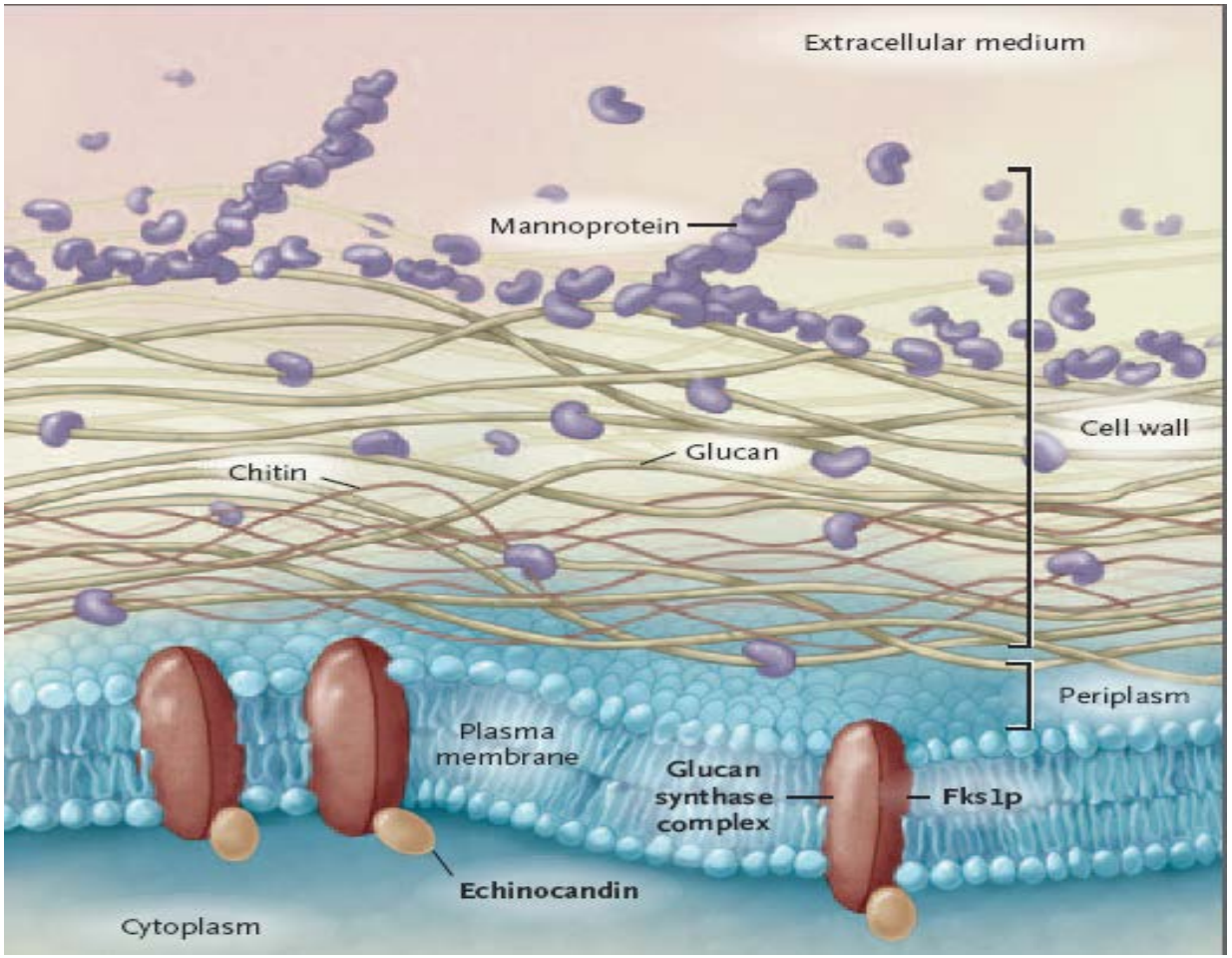
Ms B.D……/J36

Sever sepsis again

Bacteriological samples :negatives

Thoraco abdominal CT: no deep infection

Serology of candidiasis positive **antigen and antibodies**


Extracellular medium
Mannoprotein
Cell wall
Glucan
Chitin
Periplasm
Plasma membrane
Glucan synthase complex
Fks1p
Echinocandin
Cytoplasm

Mannan/Anti-mannan

- **antigen**: several studies: low Se and Sp
- **antibodies** : colonization rather than invasion + + +
- **Interest of kinetics**
- **combined antigen-antibodies** : attractive in grounds

... but more delicate in its routine interpretation.

Mikulska *et al. Critical Care* 2010, **14**:R222
http://ccforum.com/content/14/6/R222

CRITICAL CARE

RESEARCH Open Access

The use of mannan antigen and anti-mannan antibodies in the diagnosis of invasive candidiasis: recommendations from the Third European Conference on Infections in Leukemia

Conclusions

On the basis of the literature review, Mn antigen and A-Mn antibody offer diagnostic help in patients with suspected IC. Therefore, the following recommendations have been made by the Third European Conference on Infections in Leukemia (ECIL-3) members: the use of combined Mn/A-Mn is preferred over Mn or A-Mn alone for diagnosing invasive *Candida* infection, BII; combined Mn/A-Mn testing is useful for supporting the diagnosis of candidemia, CII; and combined Mn/A-Mn testing is useful for diagnosing hepatosplenic candidiasis, BIII.

B-D-Glucan

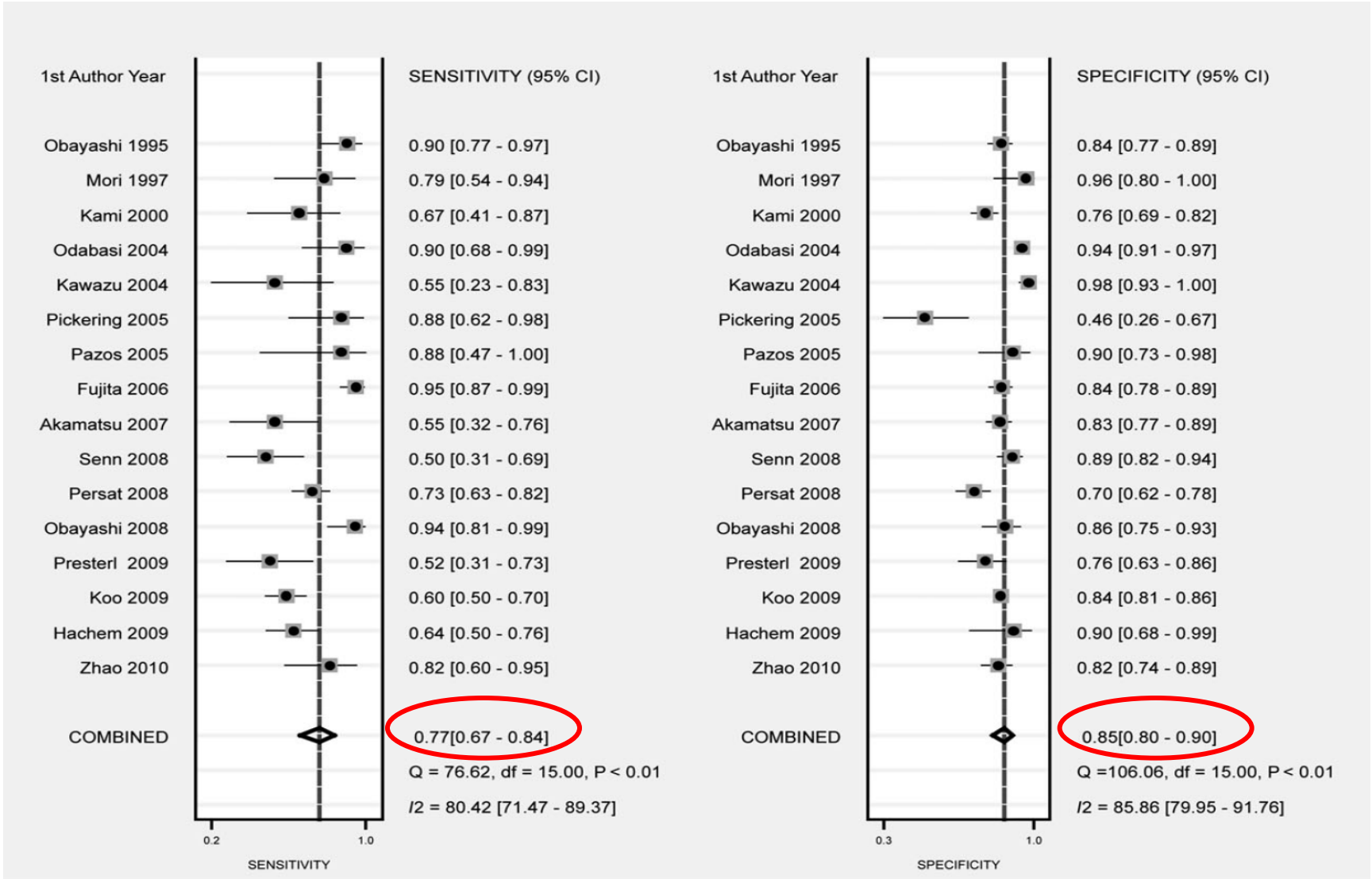
Prospective Survey of (1→3)-β-d-Glucan and Its Relationship to Invasive Candidiasis in the Surgical Intensive Care Unit Setting

John F. Mohr, Charles Sims, Victor Paetznick, Jose Rodriguez, Malcolm A. Finkelman, John H. Rex and Luis Ostrosky-Zeichner

J. Clin. Microbiol. **2011, 49(1):58. DOI:**

No. of positive BG samples	Sensitivity and specificity (%)					
	Proven (n = 3)		Proven plus probable (n = 9)		Proven plus probable plus possible (n = 15)	
	Sensitivity	Specificity	Sensitivity	Specificity	Sensitivity	Specificity
1	100	50	91	57	93	61
2	100	59	66	73	73	80
≥3	100	67	63	73	71	80

β-D-Glucan Assay for the Diagnosis of Invasive Fungal Infections: A Meta-analysis



β-D-Glucan Testing For Fungal Infections • CID 2011:52 (15 March)

DNA detection (PCR)

PCR Diagnosis of Invasive Candidiasis: Systematic Review and Meta-Analysis

Tomer Avni, Leonard Leibovici and Mical Paul
J. Clin. Microbiol. 2011, 49(2):665. DOI:

14 studies

Se= 93 % / Sp =95 %

- **SRLF 2004**: «!To confirme!»

- **IDSA 2009:**
  - Mannan/antimannan/BD Glucan:

    «!useful additions to culture methods !»

  - Real-time PCR :

    «is a non validated but intriguing methodology that holds promise as an early diagnosis aid for candidemia!»

Case report

lipid formulation of amphotericin B 3 mg/kg daily

We are waiting for contrôle of serology

Conclusion

Epidemiology and pathophysiology

Increased rate of non albicans

Diagnosis

Remains difficult,PCR ??

The molecules

Echinocandins : proeminent place

Available guidelines

Association? molecular diagnosis ?

Thank you for your attention

- Ag :plusieures etudes :Se et Sp faibles
- **Production d'Ac : reflet de colonisation et non pas d'invasion +++**
- **Intérêt de la cinetique**
- **Recherche combinée Ag / Ac :** séduisant dans son principe **Mais… plus délicate dans son interprétation en routines.**
- • **(1,3)-ß-D glucanes :** Intérêt pour discriminer (IFI ou pas d'IFI!) car VPN élevée permet d'exclure la plupart des IFI si négatif : test de screening?

Kara georgo poulos D et al. b-D glucan assay for the diagnosis of invasive fungal infections: a meta-analysis. CID, 2011, 52, 750-770.

- **Pneumonie àCandida sous ventilation mécanique?**

- 1. La présence de Candida dansles prélèvements respiratoires est rarement corrélée àdes lésions histologiques de pneumonie
- 2. Les seuils quantitatifs «significatifs»validés pour les bactéries ne le sont pas pour Candida
- 3. L'absence de traitement anti-fungique n'empêche pas la guérison
- 4. Généralement il s'agit donc d'une colonisation pouvant inciter àrechercher d'autres sites…et éventuellement àtraiter
- 5. Il existe cependant d'authentiques pneumonies àCandidahématogènes ou par inhalation

A bedside scoring system ("Candida score") for early antifungal treatment in nonneutropenic critically ill patients with *Candida* colonization*

Crit Care Med 2006 Vol. 34, No. 3

Candida score = 1 x (nutrition parentérale) + 1 x (chirurgie) + 1 x (colonisation multifocale à *Candida* sp) + 2 x (sepsis sévère)

Codage de toutes les variables : absente = 0, présente = 1

Une colonisation multifocale à *Candida* spp. est définie par plus de deux sites colonisés

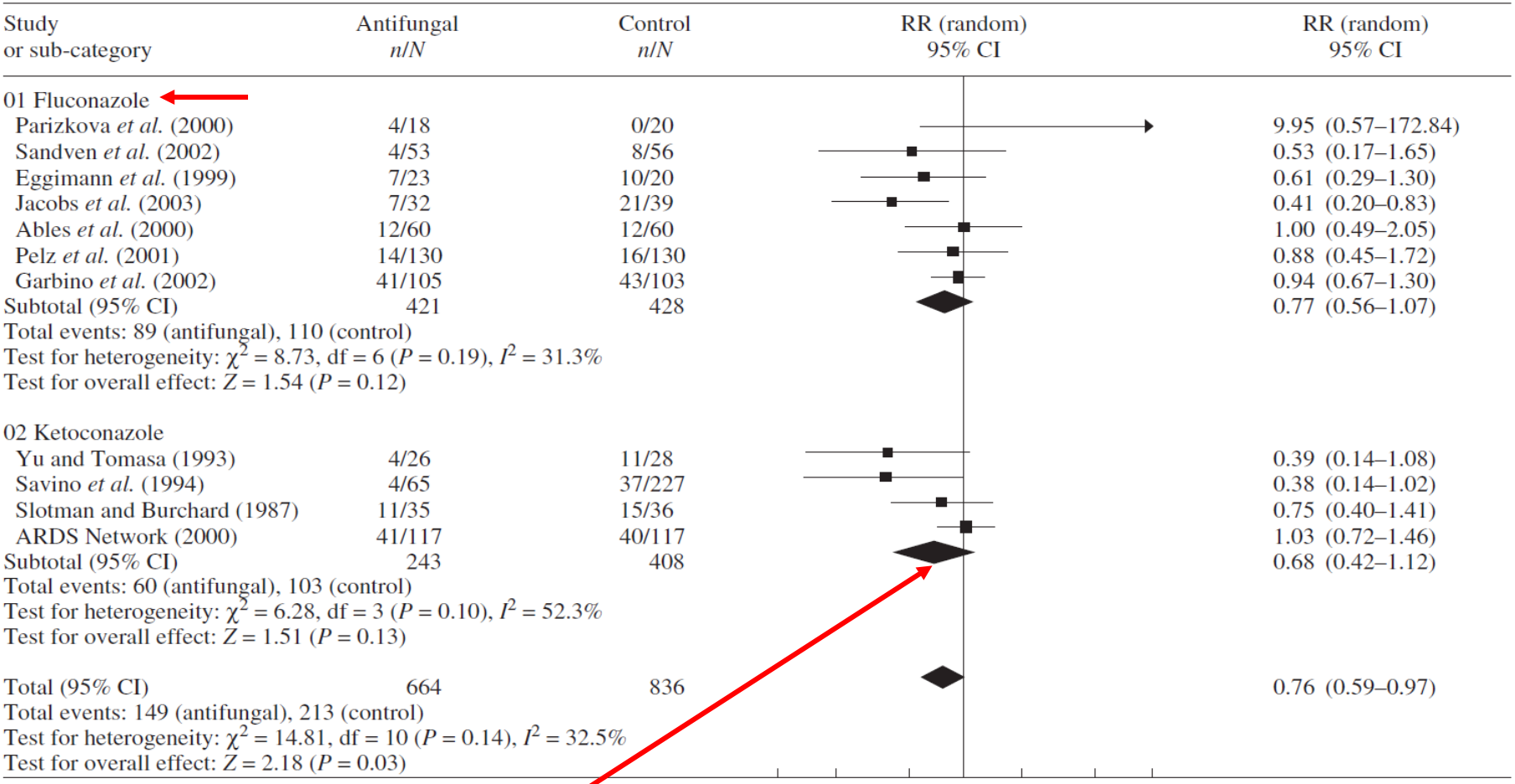
Indication à un traitement antifongique précoce : « *Candida score* » > 2,5

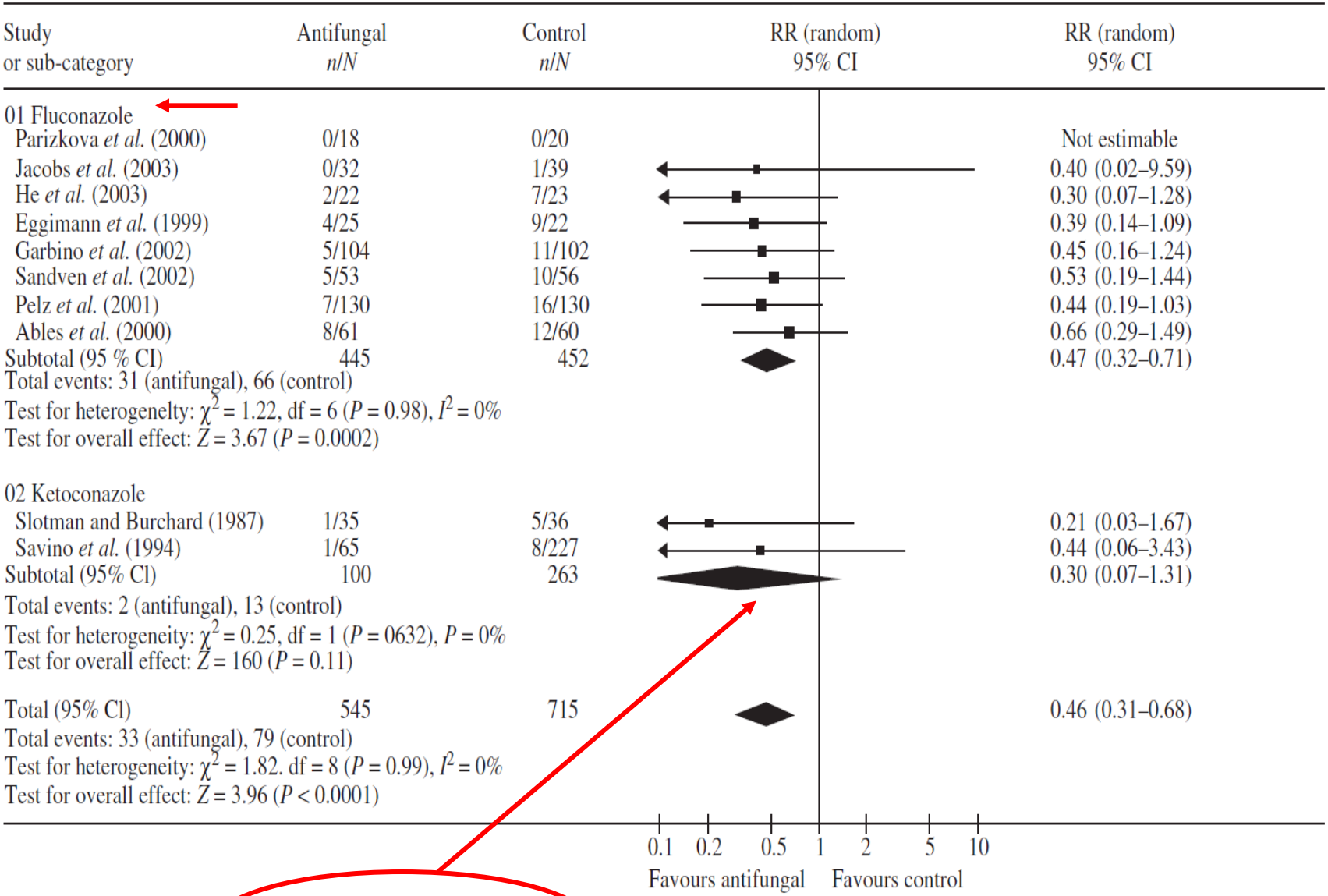
Fait Mieux :Sensibilité de 81 % et Spécificité de 74 %

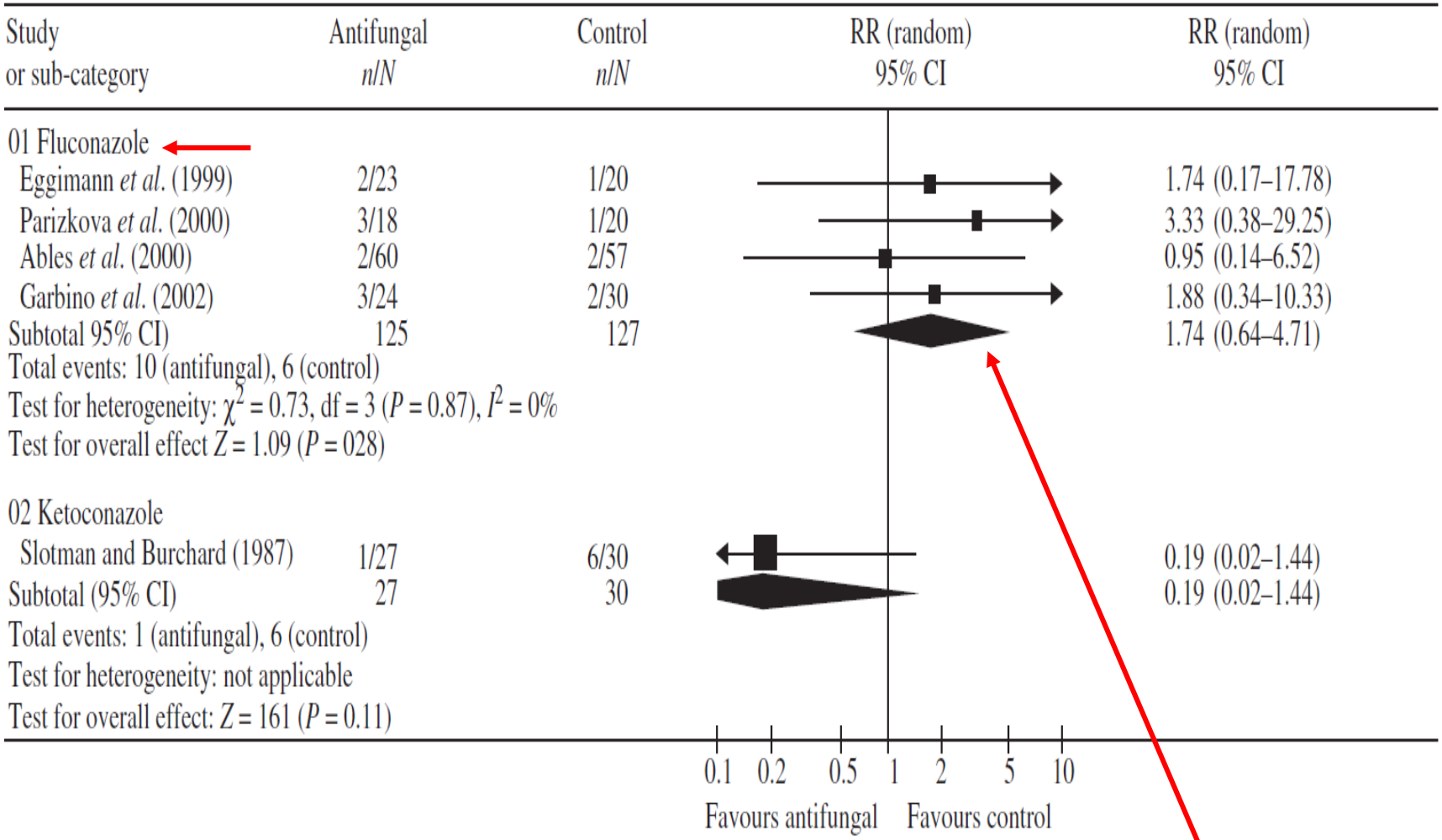
Journal of Antimicrobial Chemotherapy (2006) **57**, 628–638
doi:10.1093/jac/dki491
Advance Access publication 3 February 2006

JAC

Antifungal agents for preventing fungal infections in non-neutropenic critically ill and surgical patients: systematic review and meta-analysis of randomized clinical trials




Study or sub-category
Antifungal n/N
Control n/N
RR (random) 95% CI
RR (random) 95% CI
01 Fluconazole
Parizkova et al. (2000) 0/18 0/20 Not estimable
Jacobs et al. (2003) 0/32 1/39 0.40 (0.02–9.59)
He et al. (2003) 2/22 7/23 0.30 (0.07–1.28)
Eggimann et al. (1999) 4/25 9/22 0.39 (0.14–1.09)
Garbino et al. (2002) 5/104 11/102 0.45 (0.16–1.24)
Sandven et al. (2002) 5/53 10/56 0.53 (0.19–1.44)
Pelz et al. (2001) 7/130 16/130 0.44 (0.19–1.03)
Ables et al. (2000) 8/61 12/60 0.66 (0.29–1.49)
Subtotal (95 % CI) 445 452 0.47 (0.32–0.71)
Total events: 31 (antifungal), 66 (control)
Test for heterogenelty: χ2 = 1.22, df = 6 (P = 0.98), I2 = 0%
Test for overall effect: Z = 3.67 (P = 0.0002)
02 Ketoconazole
Slotman and Burchard (1987) 1/35 5/36 0.21 (0.03–1.67)
Savino et al. (1994) 1/65 8/227 0.44 (0.06–3.43)
Subtotal (95% CI) 100 263 0.30 (0.07–1.31)
Total events: 2 (antifungal), 13 (control)
Test for heterogeneity: χ2 = 0.25, df = 1 (P = 0632), P = 0%
Test for overall effect: Z = 160 (P = 0.11)
Total (95% CI) 545 715 0.46 (0.31–0.68)
Total events: 33 (antifungal), 79 (control)
Test for heterogeneity: χ2 = 1.82. df = 8 (P = 0.99), I2 = 0%
Test for overall effect: Z = 3.96 (P < 0.0001)
0.1 0.2 0.5 1 2 5 10
Favours antifungal
Favours control
IFI prouvée



Colonisation à C. Glabrata ou C. krusei

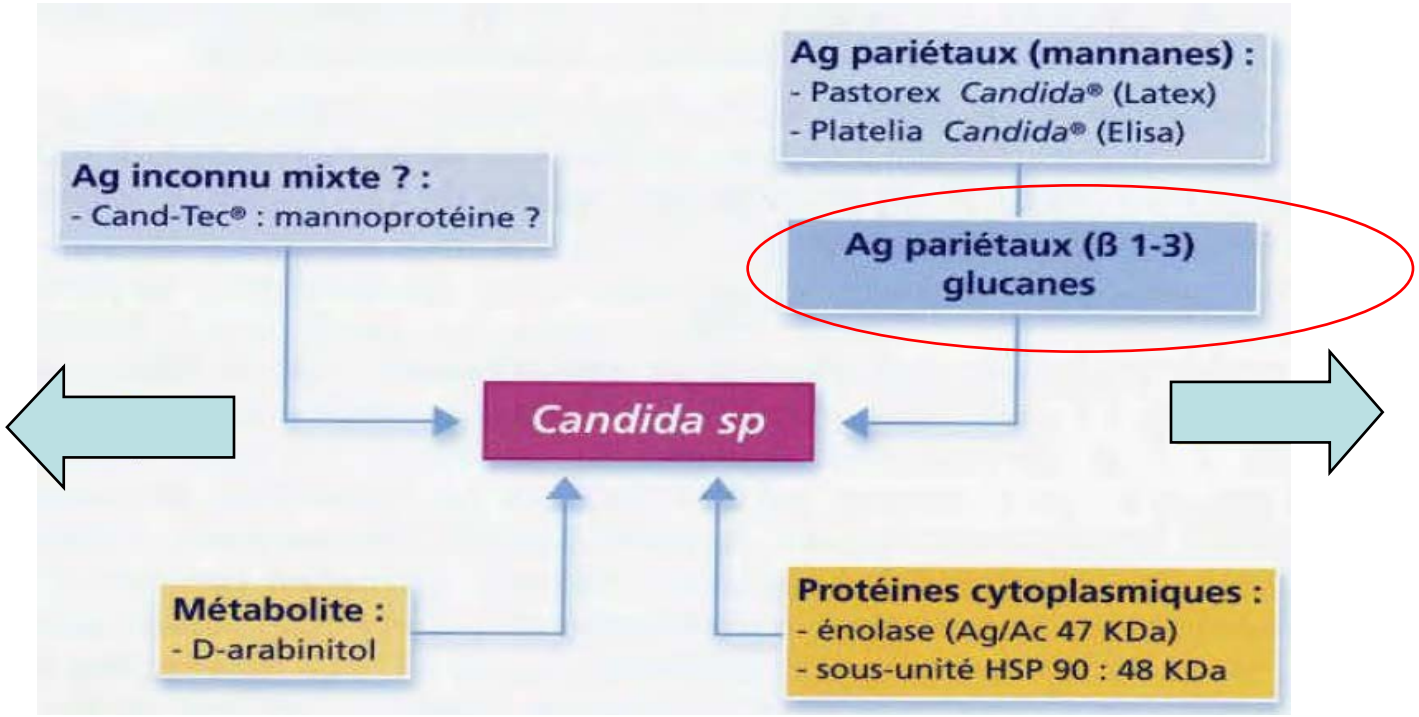
- **Traitement prophylactique :**
  population de patients, pas de prise en compte des risque individuels

- **Traitement préemptif :**
  - **traitement préventif**
  - **1 patient donné à risque élevé de développer une candidose invasive**

- **Traitement empirique :**
  - **patient suspect de présenter une candidose invasive**
  - **sans confirmation microbiologique, histologique ou sérologique**

- **Traitement curatif : mycose invasive prouvée**

Ac


Ag pariétaux (mannanes) :
- Pastorex Candida® (Latex)
- Platelia Candida® (Elisa)
Ag inconnu mixte ? :
- Cand-Tec® : mannoprotéine ?
Ag pariétaux (ß 1-3) glucanes
Candida sp
Métabolite :
- D-arabinitol
Protéines cytoplasmiques :
- énolase (Ag/Ac 47 KDa)
- sous-unité HSP 90 : 48 KDa

Ag