JOURNEES NATIONALES D'INFECTIOLOGIE 2010

SYMPOSIUM
MERCK SHARP & DOHME-CHIBRET

INFECTIONS FONGIQUES INVASIVES : STRATEGIES THERAPEUTIQUES PRECOCES

vendredi 11 juin 2010

Traitement empirique des neutropénies fébriles en hématologie

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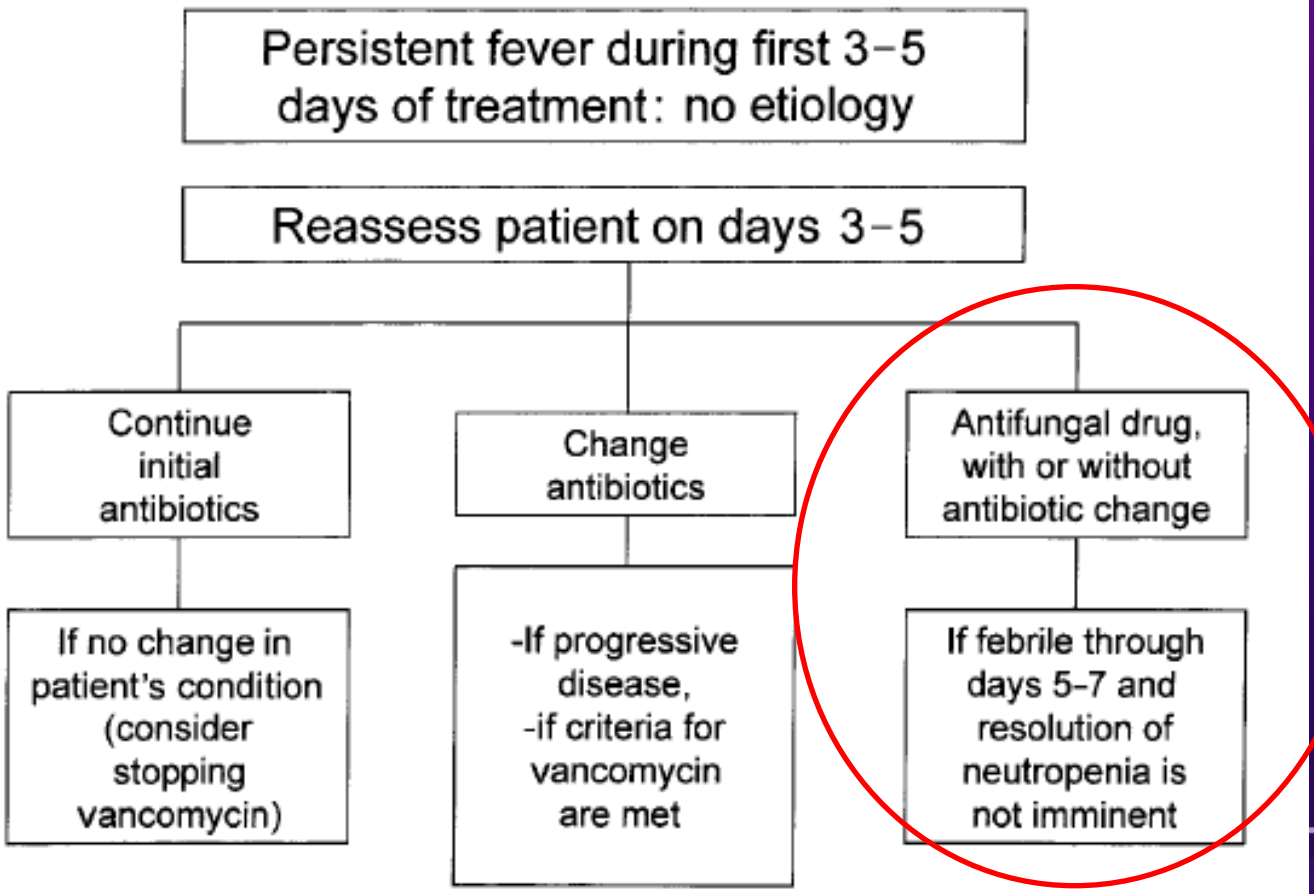
2002 Guidelines for the Use of Antimicrobial Agents in Neutropenic Patients with Cancer

Walter T. Hughes,[1] Donald Armstrong,[2] Gerald P. Bodey,[3] Eric J. Bow,[7] Arthur E. Brown,[2] Thierry Calandra,[9] Ronald Feld,[8] Philip A. Pizzo,[4,5] Kenneth V. I. Rolston,[3] Jerry L. Shenep,[1] and Lowell S. Young[6]

CID 2002:34 (15 March) • 731



Traitement antifongique empirique des neutropénies fébriles : études princeps

- Adjonction ampho B conventionnelle après J7 si fièvre persistante (Pizzo 1982, EORTC 1989) :
  - moins d'infections fongiques documentées
  - pas de ≠ sur la mortalité
  - bénéfice > si PNN < 100/mm^3, foyer localisé, pas d'antifongique prophylactique
- Méta-analyse de 24 études (2758 pts) :
  - pas d'effet du ttt antifongique sur la mortalité (amB?)
  - ↓ incidence infection fongique émergente : 1 cas prévenu pour 73 pts traités

(Gøtzsche & Johansen, *BMJ* 1997, 314: 1238)

Traitement antifongique empirique au cours des neutropénies fébriles IDSA 2002 (Hugues et al. *CID* 2002, 34 : 730-35)

- amphotéricine B conventionnelle : traitement de choix
- Alternatives :
  - formulations lipidiques d'amphotéricine B
  - fluconazole (sauf en cas de prophylaxie par les azolés, de sinusite ou de pneumopathie)
  - itraconazole

Pas de cotation…

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 30, 2004 VOL. 351 NO. 14

Caspofungin versus Liposomal Amphotericin B for Empirical Antifungal Therapy in Patients with Persistent Fever and Neutropenia

Thomas J. Walsh, M.D., Hedy Teppler, M.D., Gerald R. Donowitz, M.D., Johan A. Maertens, M.D., Lindsey R. Baden, M.D., Anna Dmoszynska, M.D., Ph.D., Oliver A. Cornely, M.D., Michael R. Bourque, M.S., Robert J. Lupinacci, M.S., Carole A. Sable, M.D., and Ben E. dePauw, M.D., Ph.D.

Antifungal Therapy in Patients with Fever and Neutropenia — More Rational and Less Empirical?

Jean Klastersky, M.D., Ph.D.

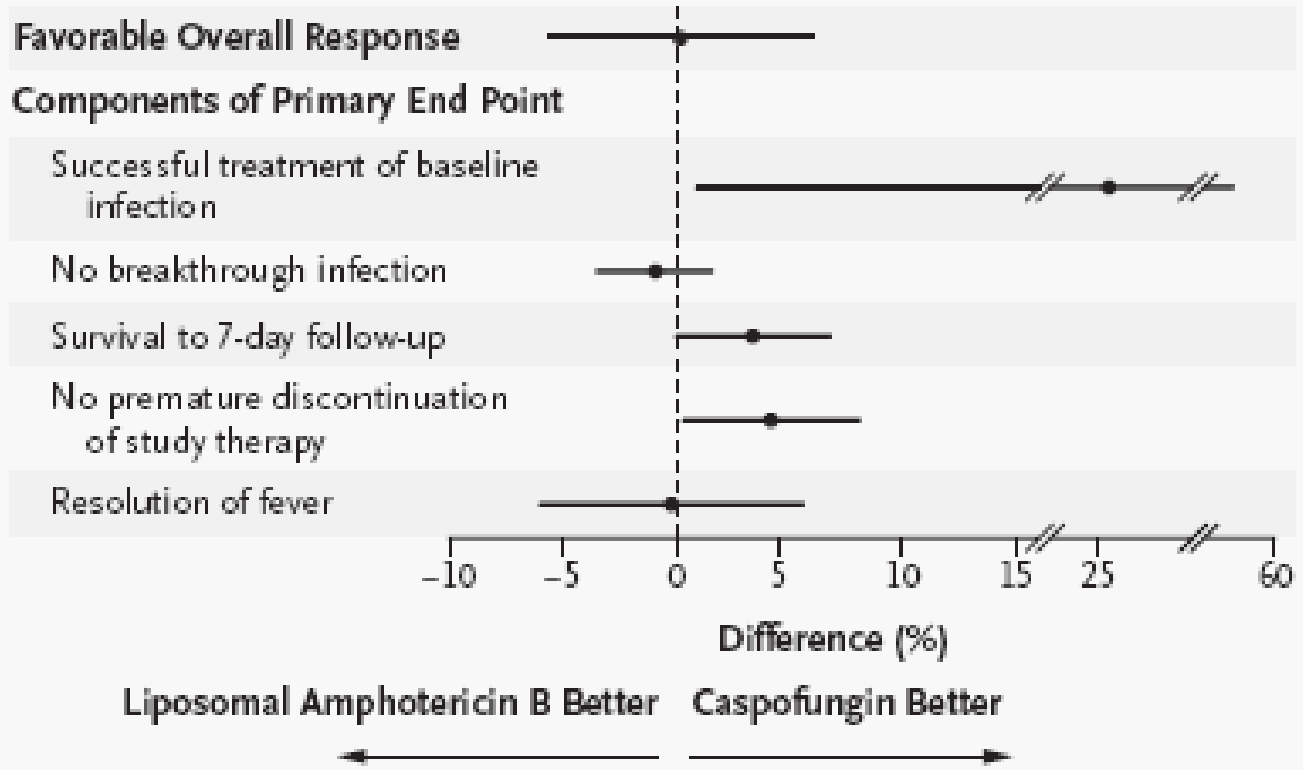
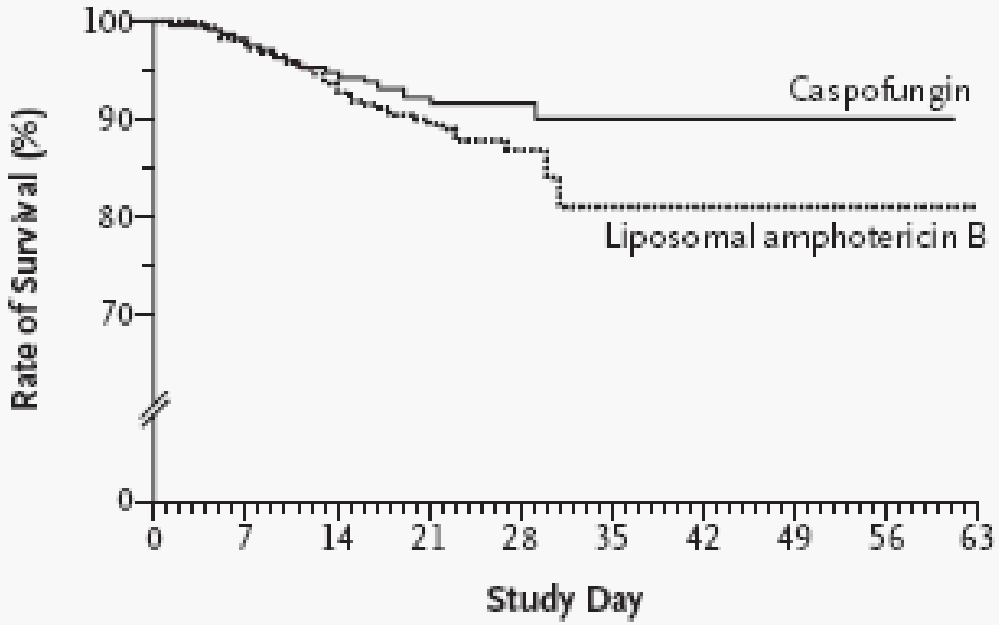


Figure 1. Differences between the Treatment Groups in the Rate of Overall Response and Components of the Primary End Point.

Differences between the treatment groups in the rate of overall response (adjusted) and individual components of the primary end point (observed) are shown, along with the 95.2 percent confidence intervals and 95 percent confidence intervals, respectively.

Walsh 2004



No. at Risk										
Caspofungin	556	547	412	192	82	37	18	13	8	6
Liposomal amphotericin B	539	523	362	185	80	38	20	10	8	6

Figure 2. Kaplan–Meier Curves Showing the Rate of Survival after Therapy in the Modified Intention-to-Treat Population, According to Treatment Group.

Log-rank chi-square=4.05 and P=0.04 for the difference in survival between patients enrolled in the caspofungin group and those enrolled in the liposomal amphotericin B group.

Walsh 2004

Table 3. Results of the Safety Analyses.

Variable	Caspofungin (N=564)	Liposomal Amphotericin B (N=547)	Difference (95% CI)*	P Value
	percent of patients		*percentage points*	
Nephrotoxicity†	2.6	11.5	−8.9 (−12.0 to −5.9)	<0.001
Infusion-related event‡	35.1	51.6	−16.4 (−22.2 to −0.7)	<0.001
Discontinuation of study therapy because of a drug-related adverse event	5.0	8.0	−3.1 (−6.0 to −0.02)	0.04
Any drug-related adverse event§	54.4	69.3	−14.9 (−20.5 to −9.2)	<0.001
Most commonly reported drug-related adverse events¶				
Clinical (any)	47.0	59.6	−12.6 (−18.4 to −6.8)	<0.001
Fever	17.0	19.4	−2.4 (−6.9 to 2.2)	
Chills	13.8	24.7	−10.9 (−15.5 to −6.2)	
Rash	6.2	5.3	0.9 (−1.8 to 3.6)	
Headache	4.3	5.7	−1.4 (−4.0 to 1.1)	
Hypokalemia	3.7	4.2	−0.5 (−2.8 to 1.8)	
Nausea	3.5	11.3	−7.8 (−10.9 to −4.7)	
Vomiting	3.5	8.6	−5.0 (−7.8 to −2.2)	
Dyspnea	2.0	4.2	−2.3 (−4.3 to −0.2)	
Flushing	1.8	4.2	−2.4 (−4.4 to −0.4)	
Laboratory (any)	22.5	32.0	−9.5 (−14.7 to −4.3)	<0.001
Increase in alanine aminotransferase	8.7	8.9	−0.1 (−3.5 to 3.2)	
Increase in aspartate aminotransferase	7.0	7.6	−0.6 (−3.7 to 2.4)	
Increase in alkaline phosphatase	7.0	12.0	−5.1 (−8.5 to −1.6)	
Decrease in potassium	7.3	11.8	−4.5 (−7.9 to −1.0)	
Increase in total bilirubin	3.0	5.2	−2.1 (−4.5 to 0.2)	
Increase in direct bilirubin	2.6	5.2	−2.6 (−5.3 to 0.2)	
Decrease in magnesium	2.3	2.6	−0.3 (−2.2 to 1.6)	
Increase in blood urea nitrogen	1.9	3.1	−1.2 (−3.9 to 1.5)	
Increase in creatinine	1.2	5.5	−4.3 (−6.4 to −2.1)	

Walsh 2004

Goldberg et al. *Eur J Cancer* 2008, 44: 2192-203

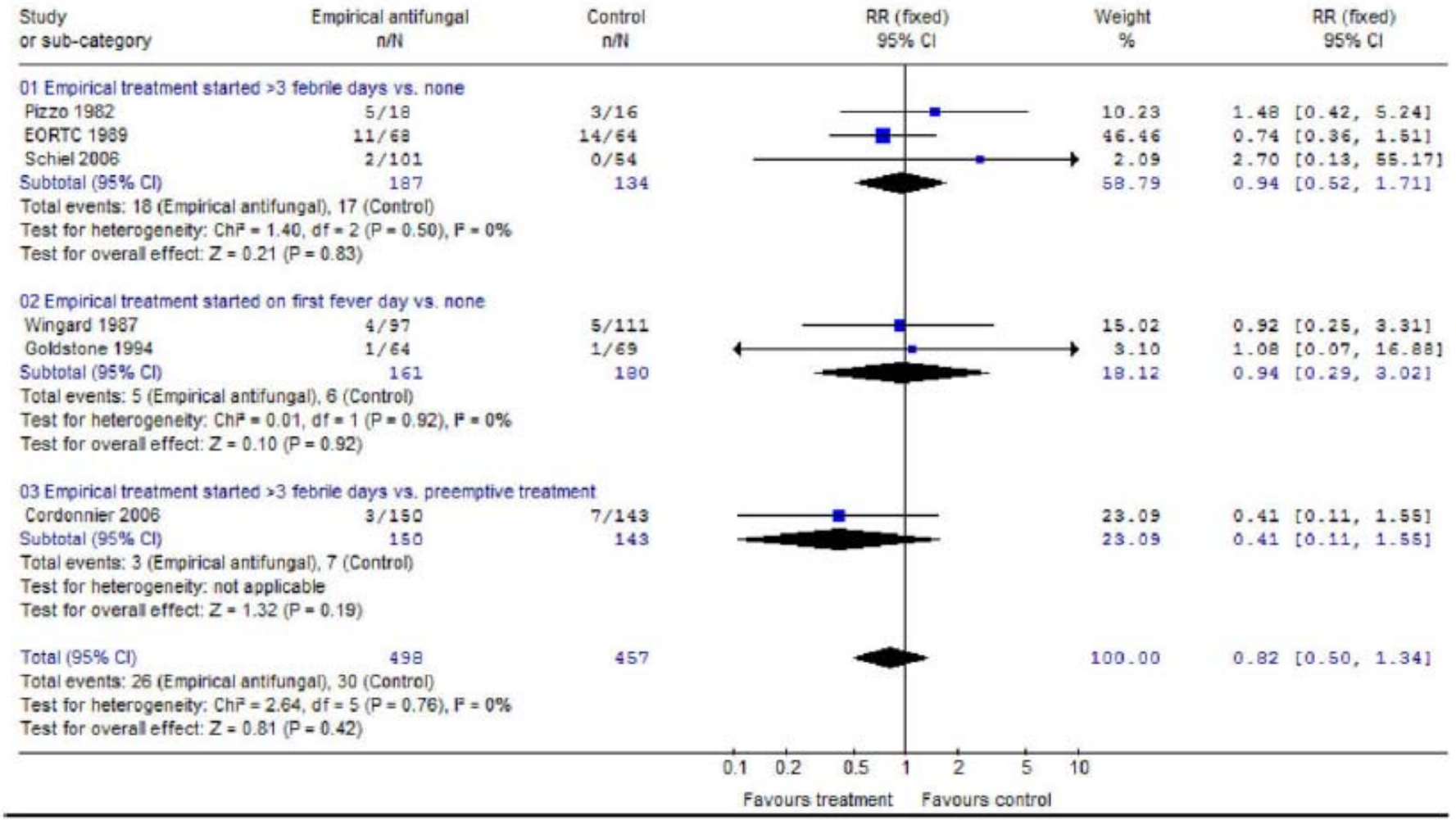


Fig. 2 - All-cause mortality for trials comparing empirical antifungal therapy versus control (placebo, no treatment or pre-emptive treatment). Studies are identified by name of first author and year of publication and sorted by their weight. Relative risks are pooled using the fixed effect model and shown on a logarithmic scale of 0.1–10.

Goldberg et al. *Eur J Cancer* 2008, 44: 2192-203

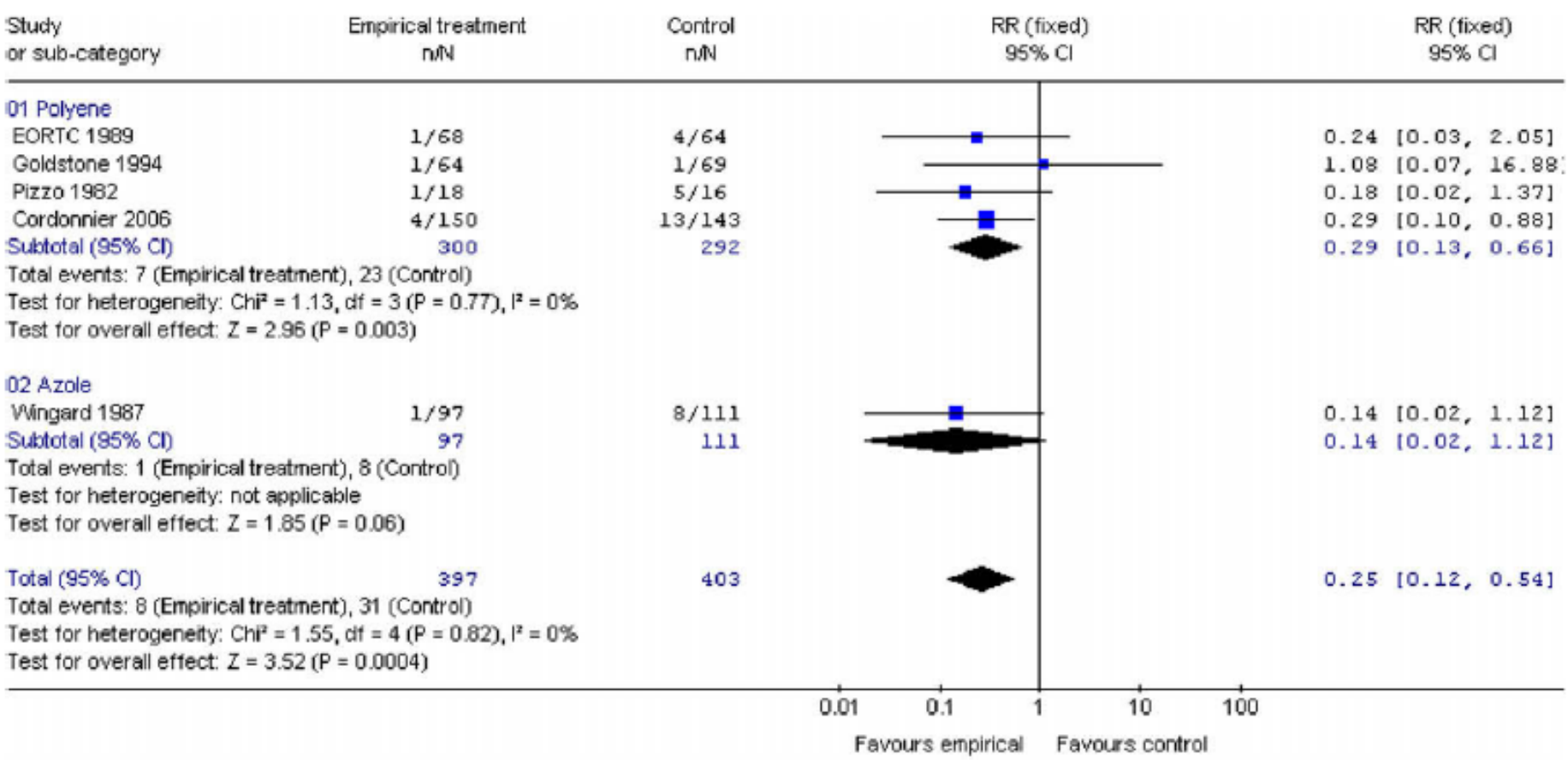


Fig. 3 – Invasive fungal infections (proven and probable) for trials comparing empirical antifungal therapy versus control (placebo, no treatment or pre-emptive treatment). Fixed effect model on a logarithmic scale of 0.01–100.

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

CID 2009:48 (1 March) • 503

Table 1. Infectious Diseases Society of America–US Public Health Service Grading System for ranking recommendations in clinical guidelines.

Category, grade	Definition
Strength of recommendation	
A	Good evidence to support a recommendation for or against use
B	Moderate evidence to support a recommendation for or against use
C	Poor evidence to support a recommendation
Quality of evidence	
I	Evidence from ≥1 properly randomized, controlled trial
II	Evidence from ≥1 well-designed clinical trial, without randomization; from cohort or case-controlled analytic studies (preferably from >1 center); from multiple time-series; or from dramatic results from uncontrolled experiments
III	Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees

NOTE. Adapted from Canadian Task Force on the Periodic Health Examination [15].

Traitement antifongique empirique au cours des neutropénies fébriles

IDSA 2009 (Pappas et al. *CID* 2009, 48 : 503-35)

- 1ère intention :
  - caspofungine ou amphotéricine B liposomale (A-I)
  - voriconazole (B-I)
- Alternatives : fluconazole ou itraconazole (B-I)
- amphotéricine B conventionnelle : « *effective alternative but there is a higher risk of toxicity*… » (A-I)
- Azolés contre-indiqués en empirique chez les patients qui en ont reçu en prophylaxie (B-II)

3rd European Conference on Infections in Leukemia

Empirical Antifungal Therapy
2009 Update of ECIL-1 / ECIL-2 Guidelines

O. Marchetti, C. Cordonnier, T. Calandra

September 25 - 26 2009, Juan-les-Pins - France

ELN European LeukemiaNet

Excellence in science EBMT European Group for Blood and Marrow Transplantation

EORTC European Organisation for Research and Treatment of Cancer

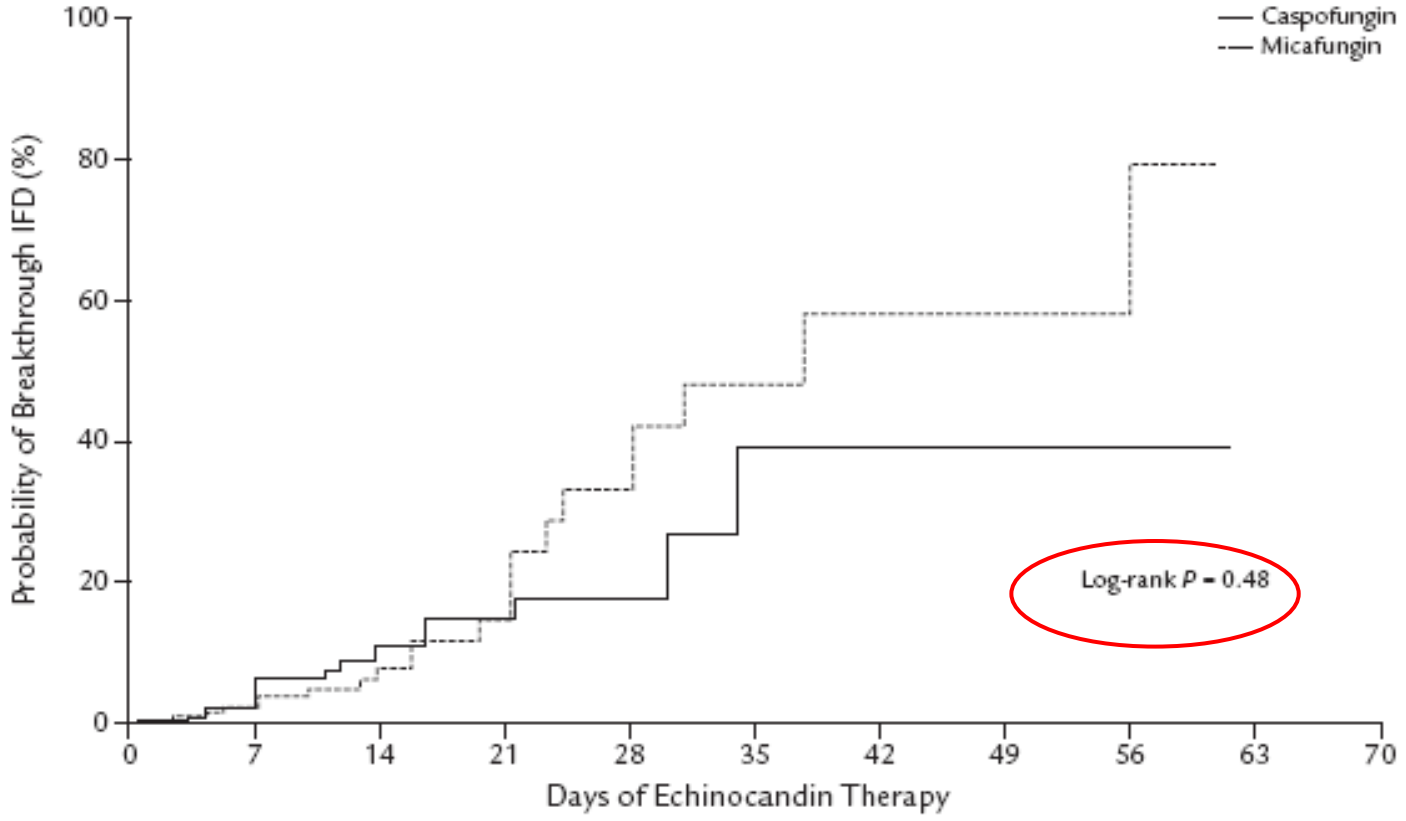
AISBL International Non-Profit Association under Belgian law IVZW

ICHS International Conference on Infections in Immunocompromised Host Society

CDC Grading system used for ECIL 1 and ECIL 2, and update ECIL 3

Quality of evidence	Strength of recommendations
I Evidence from at least one well-executed randomized trial	A Strong evidence for efficacy and substantial clinical benefit Strongly recommended
II Evidence from at least one well-designed clinical trial without randomization; cohort or case-controlled analytic studies (preferably from more than one center); multiple time-series studies; or dramatic results from uncontrolled experiments	B Strong or moderate evidence for efficacy, but only limited clinical benefit Generally recommended
III Evidence from opinions of respected authorities based on clinical experience, descriptive studies, or reports from expert committees	C Insufficient evidence for efficacy; or efficacy does not outweigh possible adverse consequences (e.g., drug toxicity or interactions) or cost of chemoprophylaxis or alternative approaches Optional
	D Moderate evidence against efficacy or for adverse outcome Generally not recommended
	E Strong evidence against efficacy or of adverse outcome Never recommended

Variable	Caspofungin (n = 149)	Micafungin (n = 174)	Risk Ratio (95% CI)	*P*
Overall favorable response, no. (%)*	122 (81.9)	141 (81.0)	0.99 (0.89–1.10)	0.96
Mortality at hospital discharge, no. (%)	12 (8.1)	13 (7.5)	0.93 (0.44–1.97)	>0.99



Clinical Therapeutics/Volume 32, Number 4, 2010

Evaluation of Caspofungin or Micafungin as Empiric Antifungal Therapy in Adult Patients With Persistent Febrile Neutropenia: A Retrospective, Observational, Sequential Cohort Analysis

David W. Kubiak, PharmD[1]; Julie M. Bryar, BA[1,2]; Anne M. McDonnell, PharmD[1]; Jorge O. Delgado-Flores, PharmD[1]; Emily Mui, PharmD[1]; Lindsey R. Baden, MD[1,3,4];

2009 UPDATE : Antifungal Drugs for Empirical Therapy

Antifungal agent	Daily dose	CDC Grading		
		Level of Recommendation	Evidence for	
			Efficacy	Safety
Liposomal AmB	3 mg/kg	A *	I	I
Caspofungin	50 mg	A *[1]	I	I
ABCD	4 mg/kg	B [2]	I	I
ABLC	5 mg/kg	B [2]	I	I
Itraconazole	200 mg iv	B [1,4]	I	I
Voriconazole	2x 3 mg/kg iv	B [1,3,4]	I	I
Micafungin	100 mg	B	II	II
AmB deoxycholate	0.5-1 mg/kg	B [2] / D [5]	I	I
Fluconazole	400 mg iv	C [1,4,6]	I	I

* A double-blind, randomized trial comparing caspofungin 50 mg/m^2 (n=56) with liposomal ampho B 3 mg/kg/d (n=25) (published in abstract form) suggests a provisional grading BII for children ; the constitution of a pediatric group specifically addressing antifungal prophylaxis and therapy in children will be considered for 2011 update of ECIL guidelines

1 No activity against mucorales

2 Infusion-related toxicity (fever, chills, hypoxia)

3 Failed the 10% non-inferiority cut-off when compared with liposomal AmB (and thus not approved by the FDA for this indication), but first-line for aspergillosis, effective therapy for candidiasis, and efficacious for prevention of breakthrough IFI.

4 Activity of azoles empirical therapy for persistent fever may be limited in patients receiving prophylaxis with an agent of the same class.

5 B in absence of / D in presence of risk factors for renal toxicity (e.g. impaired renal function at baseline, nephrotoxic co-medication including cyclosprin or tacrolimus in allogeneic HSCT recipients, aminoglycoside antibiotics, history of previous toxicity).

6 No activity against *Aspergillus* and other moulds. Not approved by the FDA for this indication.

TRAITEMENT EMPIRIQUE vs PRE-EMPTIF (Cordonnier et al. *CID* 2009, 48 : 1042-51)

- Étude prospective multicentrique ouverte, non infériorité
- Empirique (fièvre persistante) vs pré-emptif (clinique, imagerie, Ag aspergillaire)
- 293 pts, durée médiane de neutropénie 18 j
- Amphotéricine B conventionnelle ou Ambisome®
- Sous traitement pré-emptif :
  - ↑ incidence des IFI;
  - pas de ≠ sur la mortalité globale à J14 de la sortie d'aplasie
  - surmortalité dans le sous-groupe «chimio d'induction »?

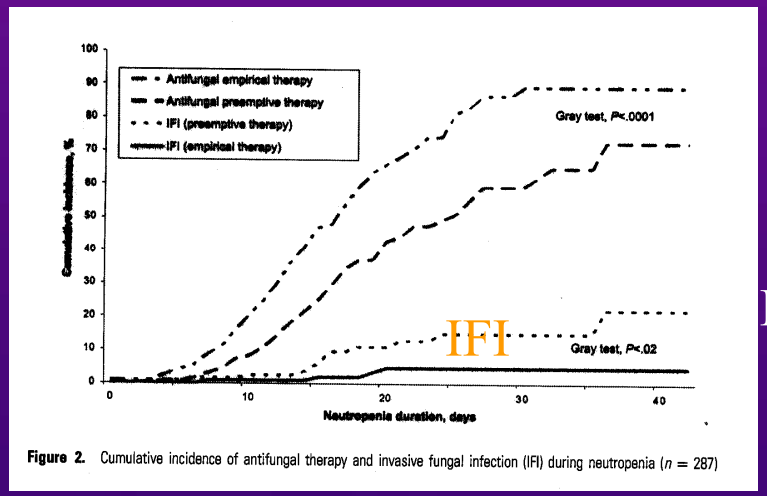


Figure 2. Cumulative incidence of antifungal therapy and invasive fungal infection (IFI) during neutropenia (n = 287)

E
PE

PE
E

(On ne peut exclure que la mortalité soit inférieure dans le groupe «empirique/induction»)

Perspective (4e trimestre 2010)

EORTC
European Organisation for Research and Treatment of Cancer

AISBL International Non-Profit Association under Belgian law IVZW

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EORTC Infectious Disease Group

FEASIBILITY FORM: EORTC trial "65091-06093"

Projected Start: Q4, 2010

"Empirical versus pre-emptive antifungal therapy of patients with haematological malignancies. A therapeutic phase III strategy study"

CONCLUSIONS

- Le traitement antifongique empirique demeure recommandé, chez les patients d'hématologie avec des durées de neutropénie prolongées qui restent fébriles sous antibiothérapie à large spectre
- La caspofungine ou l'amphotéricine B liposomale sont recommandées en 1e intention
- La place des autres molécules en 1e intention et des autres approches (en particulier du traitement pré-emptif) reste à définir