Antifungals: a different approach in other populations?

Eric Van Wijngaerden
Inwendige Ziekten - Infectieziekten

UZ Leuven | Herestraat 49 B - 3000 Leuven | www.uzleuven.be tel. +32 16 33 22 11 | UNIVERSITY HOSPITALS LEUVEN

Antifungals in non-hematological patients

- Invasive aspergillosis (IA)
- Invasive candidosis

IA in non-hematological patients

- IA in SOT patients
- IA in other diseases with congenital or acquired immune deficiency (CGD, AIDS, immunosuppressive therapy…)
- IA in the ICU:
  - 64% of proven/probable: non-hemato

Meersseman, Am J Resp CCM 2004

Antifungals for IA in non-hemato

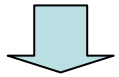
- No data from RCT's: *eg Herbrecht 2002*
  - 26 vor / 19 AmB: response 50 vs 32% (NS)
- Extrapolate "vorico first choice"?

Antifungals for IA in non-hemato

- Differences in patient population include
  - Severity of illness
  - Organ failure
  - Concomitant meds
  - Late Dx
    - Sens/spec of diagnostics (lab, CT)
    - Index of suspicion
    - Very broad DD

Voriconazole pharmacokinetics

Voriconazole serum levels: high interindividual variability!



!Difficult pharmacokinetics!

- Non-linear kinetics: saturable metabolism
  - Disproportional increase in plasma levels if dosage increased
  - Half-life = dose dependent
- Genetic polymorphism CYP2C19
  - 3 genotypes: extensive metabolizers, heterozygous extensive metabolizers, poor metabolizers
  - Plasma levels up to 2-fold (HEM) or 4- fold (PM) higher!

Purkins AAC 2002

Voriconazole IV: cyclodextrin

- Nephrotoxicity of cyclodextrin, a solubilizer
  - in patients with moderate to severe renal failure (CrCl < 50 ml/min): accumulation of SBECD with potential nephrotoxicity
  - frequent problem in ICU patients:
    - switch to oral formulation?

Von Mach, BMC Clin Pharamacol 2006; 6:6

Voriconazole pharmacokinetics

- Oral administration: standard dose generally lower than IV
  - 75 kg: 2x300 IV to 2 x 200 PO?
- When is absorption “normal” in an ICU patient?
- Oral bio-availability affected if taken with food
  - reduction oral bio-availability with > 20%! Purkins Br J Clin Pharm 2003
  - no studies if administered with enteral feeding on ICU
    - Stop enteral feeding 1hr before to 2 hrs after administration?
    - Administration 2x daily: 6 hrs without calory intake!

Voriconazole pharmacokinetics

- Extensive CYP-metabolism: drug interactions!
  - Other drugs affecting voriconazole plasma levels
    - Contra-indicated with potent inducers
      - » Rifampicin, ritonavir, carbamazepine, phenobarbital
    - Dose adjustments needed with phenytoin (5 mg/kg bid)
  - Voriconazole affecting plasma levels of others (inhibition)
    - Contra-indicated with sirolimus, astemizole, cisapride, …
    - Dose adjustments needed if combined with
      - » Cyclosporin, tacrolimus

Voriconazole therapeutic drug monitoring?

- Serum levels correlated with efficacy/safety?

FDA report	- no correlation
Smith. AAC 2006; 50:1570-2.	- 28 patients, random plasma samples - progressive disease in 18 patients with levels < 2.05 µg/ml
Trifilio S. BMT 2007; 40:451-6.	- 71 patients, trough plasma levels - 6 breakthrough candidiasis in patients with levels < 2 µg/ml
Denning D. CID 2002; 34: 563-71.	- liver failure or liver toxicity in 6/22 patients with levels > 6 µg/ml

- Optimal serum levels: 2-6 µg/ml
  - Well above MIC of Aspergillus/Candida spp.

Voriconazole therapeutic drug monitoring?

- TDM voriconazole
  - 52 adult patients: 181 samples
  - 25%: levels < 1mg/L
    - Correlated with oral therapy
    - Lack of response more frequent in this group
  - 31%: levels > 5.5 mg/L
    - Correlated with omeprazole comedication
    - 5 patients with encephalopathy
      - 4 of 5 treated intravenously
  - TDM could improve efficacy and safety
  - Proposed therapeutic interval 1-5.5 µg/ml

Pascual A. CID 2008;46:201-211.

Caspofungin TDM in critically ill patients

Caspofungin plasma concentrations in SICU patients

- Trough concentrations in 40 SICU patients
- Results:

  Trough levels: 0.52-4.08 µg/ml

  - Healthy volunteers: 1.12-1.78 µg/ml (Stone AAC 2002, 46, 739)
- Higher in patients with low body weight (< 75 kg)
- Higher in patients with albumin concentration > 23.6 g/L

! Patients' body weight varied from 48 – 108 kg >< every patient got LD 70 mg/ MD 50 mg!

Nguyen TH et al. JAC 2007; 60:100-106.

Antifungals for IA in non-hemato

- Voriconazole first choice
  - often problematic
  - optimal dosing not established: TDM?
- Caspofungin: optimal dosing: TDM?
  - Probably also other candins, little data
- L-AmB, less side effects than AmB
  - But still..
- (Posaconazole: PO, PK, CYP…)

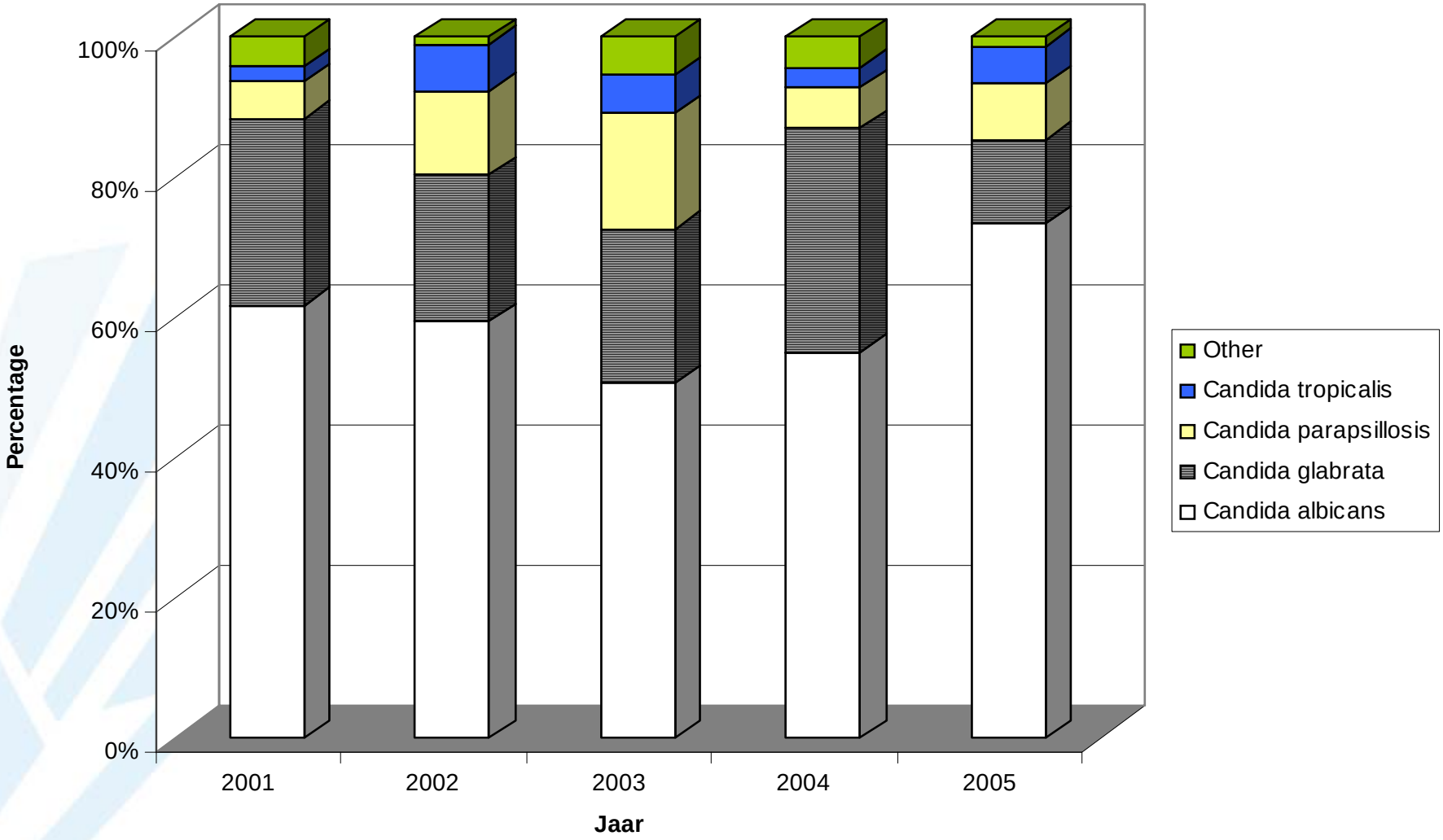
Invasive candidiasis

Table 3. General patterns of susceptibility of *Candida* species.

Candida species	Fluconazole	Itraconazole	Voriconazole[d]	Flucytosine	Amphotericin B	Candins[a]
C. albicans	S	S	S	S	S	S
C. tropicalis	S	S	S	S	S	S
C. parapsilosis	S	S	S	S	S	S (to I?)
C. glabrata	S-DD to R[b]	S-DD to R[c]	S to I[d]	S	S to I[e]	S
C. krusei	R	S-DD to R[c]	S to I[d]	I to R	S to I[e]	S
C. lusitaniae	S	S	S	S	S to R[f]	S

Pappas, CID 2004;38,161

Fungemia in UZ Leuven



Lagrou, Eur J Clin Microbiol Infect Dis 2007, 26: 514.

Gevoeligheid *Candida* UZ Leuven

	Fluconazole			Voriconazole	Caspofungine	Amfotericine B
Species (n)	S	SDD	R	S	MIC ≤ 1 µg/mL	MIC ≤ 1 µg/mL
C. albicans (42)	100%			100%	100%	100%
C. glabrata (11)	18%	73%	9%	100%	100%	100%
C. parapsilosis (5)	100%			100%	100%	100%
Totaal (62)	83,9%	14,5%	1,6%	100%	100%	100%

Juni 2004-juni 2005

Gevoeligheidsbepaling met YeastOne colorimetric plate (Trek diagnostic Systems)

Lagrou, Eur J Clin Microbiol Infect Dis 2007, 26: 514.

Candidemia

- Fluconazole as effective as but less toxic than AmB in non-neutropenic pts

Rex et al. NEJM 1994; 331:1325-30

Published Candidemia Studies
(Endpoints and Success Rates)

Study	Design	Efficacy endpoint	Assessed by	Success rate (cured + improved)	Overall mortality
Candidemia 1 (Rex, 1994)	Fluconazole vs Amphotericin B	Variable: up to 12-week follow-up	DRC	70% vs 79%	33% vs 40%
Candidemia 2 (Rex, 2003)	Fluconazole vs Amphotericin B + fluconazole	Variable: up to 12-week follow-up	DRC	56% vs 69%	39% vs 40%
Caspofungin (Mora-Duarte, 2002)	Caspofungin vs Amphotericin B	Fixed: end of IV therapy	Investigator	73% vs 62%	30% vs 34%
Itraconazole (Tuil, 2003; ISICEM)	Fluconazole vs Itraconazole	Fixed: 12-week follow-up	Investigator	41% vs 35%	40%
Global Candidemia Study 150-608	Voriconazole vs Amphotericin B→ fluconazole	Fixed: 12-week follow-up	DRC	41% vs 41%	36% vs 42%
		Variable: up to 12-week follow-up	DRC	65% vs 71%	

Caspofungin for invasive candidiasis

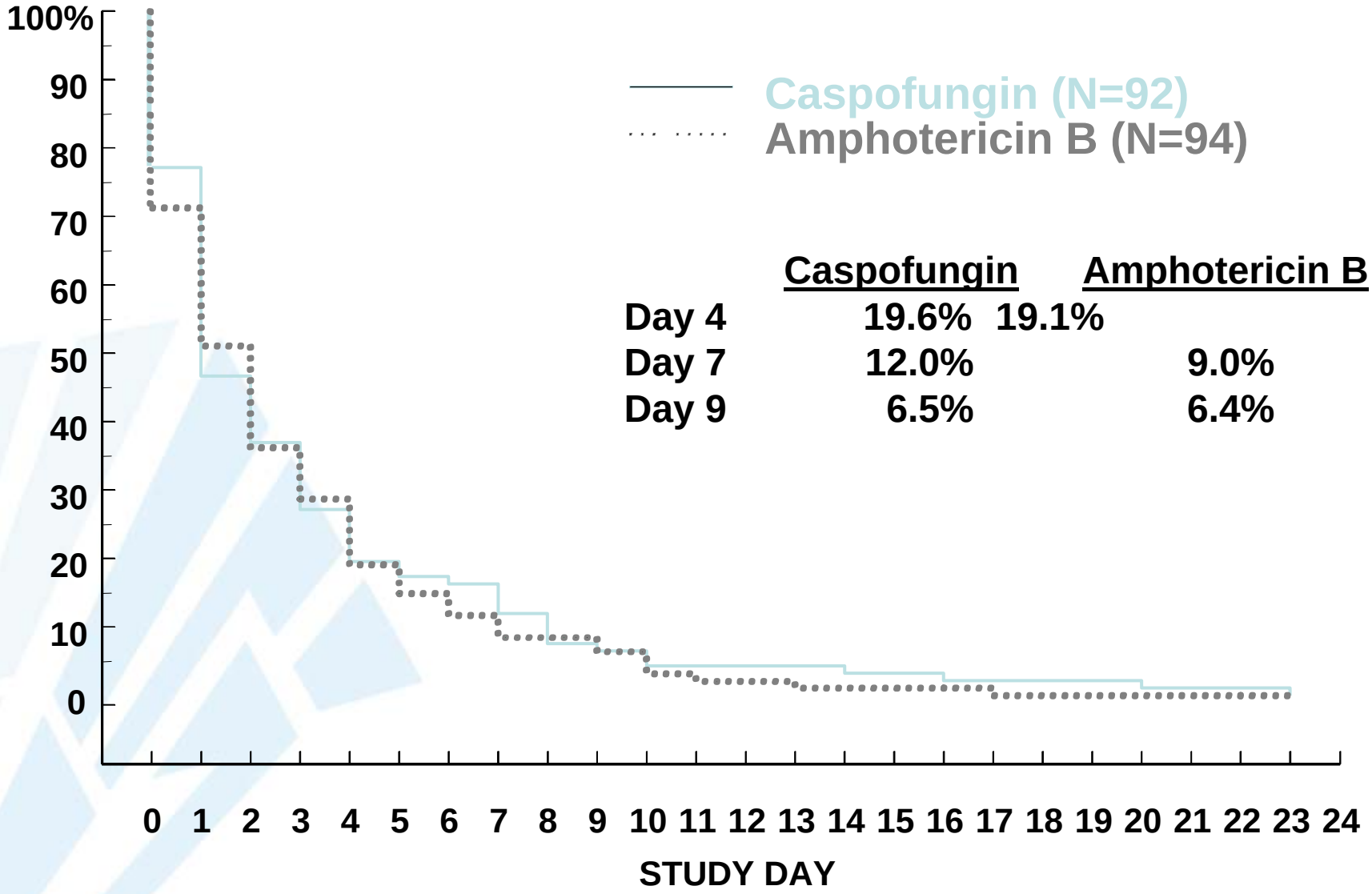
	Caspofungin 70/50 mg n (%)	Amphotericin B 0.6-1.0 mg/kg n (%)	Estimated Difference Adjusted for Strata % (95.6% CI; *P*)
Success (MITT) n=224	80/109 (73%)	71/115 (62%)	12.7% (–0.7, 26.0; P=0.09)
Evaluable Patients n=185	71/88 (81%)	63/97 (65%)	15.4% (1.1, 29.7; P=0.04)
Crude Mortality	39 (34%)	38 (30%)	P=0.53

Mora-Duarte et al. N Engl J Med 2002

TABLE 6. DRUG-RELATED ADVERSE EVENTS AND OTHER SAFETY END POINTS.

VARIABLE	CASPOFUNGIN (N=114)	AMPHOTERICIN B (N=125)	P VALUE
	no./total no. (%)		
Clinical events	33/114 (28.9)	73/125 (58.4)	0.002
Chills	6/114 (5.3)	33/125 (26.4)	0.003
Fever	8/114 (7.0)	29/125 (23.2)	0.01
Hypertension	2/114 (1.8)	8/125 (6.4)	
Phlebitis or thrombophlebitis	4/114 (3.5)	6/125 (4.8)	
Tachycardia	2/114 (1.8)	13/125 (10.4)	
Nausea	2/114 (1.8)	7/125 (5.6)	
Vomiting	4/114 (3.5)	10/125 (8.0)	
Tachypnea	0/114	13/125 (10.4)	
Rash	1/114 (0.9)	4/125 (3.2)	
Laboratory abnormalities*	27/111 (24.3)	67/124 (54.0)	0.002
Elevated serum alanine aminotransferase	4/109 (3.7)	10/123 (8.1)	
Elevated serum aspartate aminotransferase	2/108 (1.9)	11/122 (9.0)	
Elevated serum alkaline phosphatase	9/109 (8.3)	19/122 (15.6)	
Elevated total serum bilirubin	3/109 (2.8)	11/124 (8.9)	
Elevated blood urea nitrogen	2/108 (1.9)	19/120 (15.8)	0.02
Elevated serum creatinine	4/109 (3.7)	28/124 (22.6)	0.05
Decreased serum potassium	11/111 (9.9)	29/124 (23.4)	0.04
Decreased hemoglobin	1/111 (0.9)	13/124 (10.5)	
Clinical event or laboratory abnormality	48/114 (42.1)	94/125 (75.2)	0.002
Withdrawal because of adverse event	3/114 (2.6)	29/125 (23.2)	0.003
Infusion-related event	23/114 (20.2)	61/125 (48.8)	0.002
Hypokalemia requiring supplementation within 72 hr after onset	13/114 (11.4)	33/125 (26.4)	0.02
Nephrotoxic effect†	8/95 (8.4)	26/105 (24.8)	0.02

Time to First Negative Blood Culture



	Caspofungin	Amphotericin B
Day 4	19.6%	19.1%
Day 7	12.0%	9.0%
Day 9	6.5%	6.4%

Mora-Duarte et al. N Engl J Med 2002

Micafungin vs liposomal AmB

	Micafungin		Liposomal amphotericin B		Difference in proportion (95% CI)
	Number of patients	Number treated successfully (%)	Number of patients	Number treated successfully (%)	
Overall	247	183 (74·1%)	247	172 (69·6%)	4·5% (−3·5 to 12·4)
Complete response*		159 (64·4%)		150 (60·7%)	
Partial response*		24 (9·7%)		22 (8·9%)	
Neutropenic status at baseline					4·9% (−3·0 to 12·8)†
<500 cells per μL	32	19 (59·4%)	25	14 (56·0%)	
≥500 cells per μL	215	164 (76·3%)	222	158 (71·2%)	

*Both mycological eradication and a complete clinical response were necessary to be deemed a complete response. For a partial response, an improvement in clinical symptoms and any radiographic abnormalities had to be demonstrated in addition to a mycological response. †Stratified by neutropenic status.

Table 3: Treatment success in the modified intention-to-treat population

Kuse Lancet 2007; 369, 1519

Micafungin vs caspofungin

Table 3. Treatment success for the modified intent-to-treat population.

Variable	Micafungin arms		Caspofungin arm (n = 188)
	100 mg arm (n = 191)	150 mg arm (n = 199)	
Duration of therapy, median days (range)[a]	14 (1.0–61.0)	14 (1.0–56.0)	14 (1.0–43.0)
Treatment success[b]			
Investigators	146 (76.4)	142 (71.4)	136 (72.3)
Data review panel	139 (72.8)	139 (69.8)	133 (70.7)
Clinical success			
Overall	167 (87.4)	174 (87.4)	164 (87.2)
Candidemic[c]			
Complete response	128/163 (78.5)	136/168 (81.0)	123/161(76.4)
Partial response	15/163 (9.2)	12/168 (7.1)	21/161 (13.0)
Noncandidemic			
Complete response	14/28 (50.0)	17/30 (56.7)	15/26 (57.7)
Partial response	10/28 (35.7)	9/30 (30.0)	5/26 (19.2)
Mycological success	169 (88.5)	166 (83.4)	158 (84.0)

Pappas CID 2007, 45, 883

Micafungin and the liver?

4.4 Special warnings and precautions for use

Hepatic effects:
The development of foci of altered hepatocytes (FAH) and hepatocellular tumours after a treatment period of 3 months or longer were observed in rats. The assumed threshold for tumour development in rats is approximately in the range of clinical exposure. The relevance of this finding for the therapeutic use in patients can not be excluded. Liver function should be carefully monitored during micafungin treatment. To minimise the risk of adaptive regeneration and potentially subsequent liver tumour formation, early discontinuation in the presence of significant and persistent elevation of ALT/AST is recommended. Micafungin treatment should be conducted on a careful risk/benefit basis, particularly in patients having severe liver function impairment or chronic liver diseases known to represent preneoplastic conditions, such as advanced liver fibrosis, cirrhosis, viral hepatitis, neonatal liver disease or congenital enzyme defects, or receiving a concomitant therapy including hepatotoxic and/or genotoxic properties.

"Micafungin treatment was associated with significant impairment of liver function (increase of ALT,AST or total bilirubin > 3 times ULN) in both healthy volunteers and patients. In some patients more severe hepatic dysfunction, hepatitis, or hepatic failure including fatal cases have been reported".

Anidulafungin vs Fluconazole Candidemia Treatment Study

- Randomized, double blind, multinational study
  - Anidulafungin 200/100 mg IV QD; or
  - Fluconazole 800/400 mg IV QD
- IV study treatment for at least 10 days
- Primary endpoint: response at end of IV

Reboli, NEJM 2007

Global response

End Point	Global Success: Fluconazole Group (N=118) no. (%)	Global Success: Anidulafungin Group (N=127) no. (%)	Absolute Percent Difference between Treatments (95% CI)
End of intravenous therapy	71 (60.2)	96 (75.6)	15.4 (3.9 to 27.0)
End of all therapy	67 (56.8)	94 (74.0)	17.2 (5.5 to 29.0)
2-Week follow-up	58 (49.2)	82 (64.6)	15.4 (3.1 to 27.7)
6-Week follow-up	52 (44.1)	71 (55.9)	11.8 (−0.6 to 24.3)

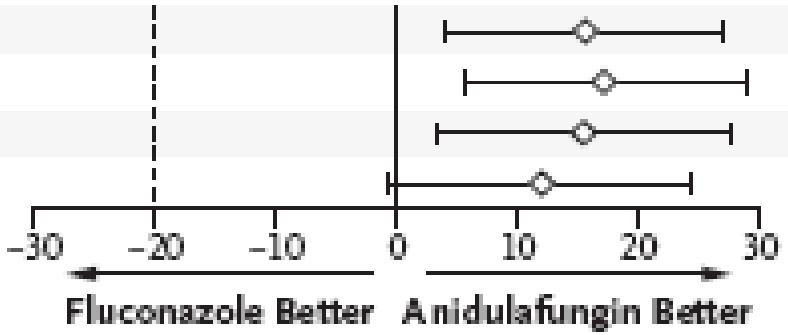


Figure 1. Global Response to Treatment for Prespecified Time Points in the Modified Intention-to-Treat Population.

Reboli, NEJM 2007

Global response per species

Table 3. Microbiologic and Global Responses at the End of Intravenous Therapy in the Modified Intention-to-Treat Population.*

Candida Pathogen	Successful Microbiologic Response			Successful Global Response†		
	Anidulafungin Group	Fluconazole Group	P Value	Anidulafungin Group	Fluconazole Group	P Value
	no. of isolates/total no. (%)			*no. of patients/total no. (%)*		
Candida albicans	77/81 (95)	57/70 (81)	0.01	60/74 (81)	38/61 (62)	0.02
C. glabrata	15/20 (75)	18/30 (60)	0.37	9/16 (56)	11/22 (50)	0.75
C. parapsilosis	9/13 (69)	14/16 (88)	0.36	7/11 (64)	10/12 (83)	0.37
C. tropicalis	13/15 (87)	7/11 (64)	0.35	13/14 (93)	4/8 (50)	0.04
Other candida species	5/6 (83)	3/3 (100)	1.00	3/4 (75)	2/3 (67)	1.00
All candida species	119/135 (88)	99/130 (76)	0.02	92/119 (77)	65/106 (61)	0.01

Reboli, NEJM 2007

In conclusion, this study shows that anidulafungin is not inferior to and possibly is more efficacious than fluconazole for the primary treatment of the candidemic form of invasive candidiasis, with a safety profile similar to that of fluconazole…

Reboli, NEJM 2007

Candidemia treatment trials

- “A is non-inferior to B”

- Anidulafungin (or candins?) may clear *Candida* quicker than fluconazole (and so does ampho B)

Candidemia treatment trials

- No demonstrated difference in
  - Mortality
  - Late secundary foci (bone, eye, heart…)

Candida IDSA guidelines 2008

- Candidemia, non neutropenic
  - Fluconazole
  - Candin if
    - severe disease or
    - exposure to azole
  - Switch candin to fluco if susceptible and stable
- Candidemia, neutropenic
  - Candin or L-AmB

Pappas, ICAAC 2007

Candida IDSA guidelines 2008

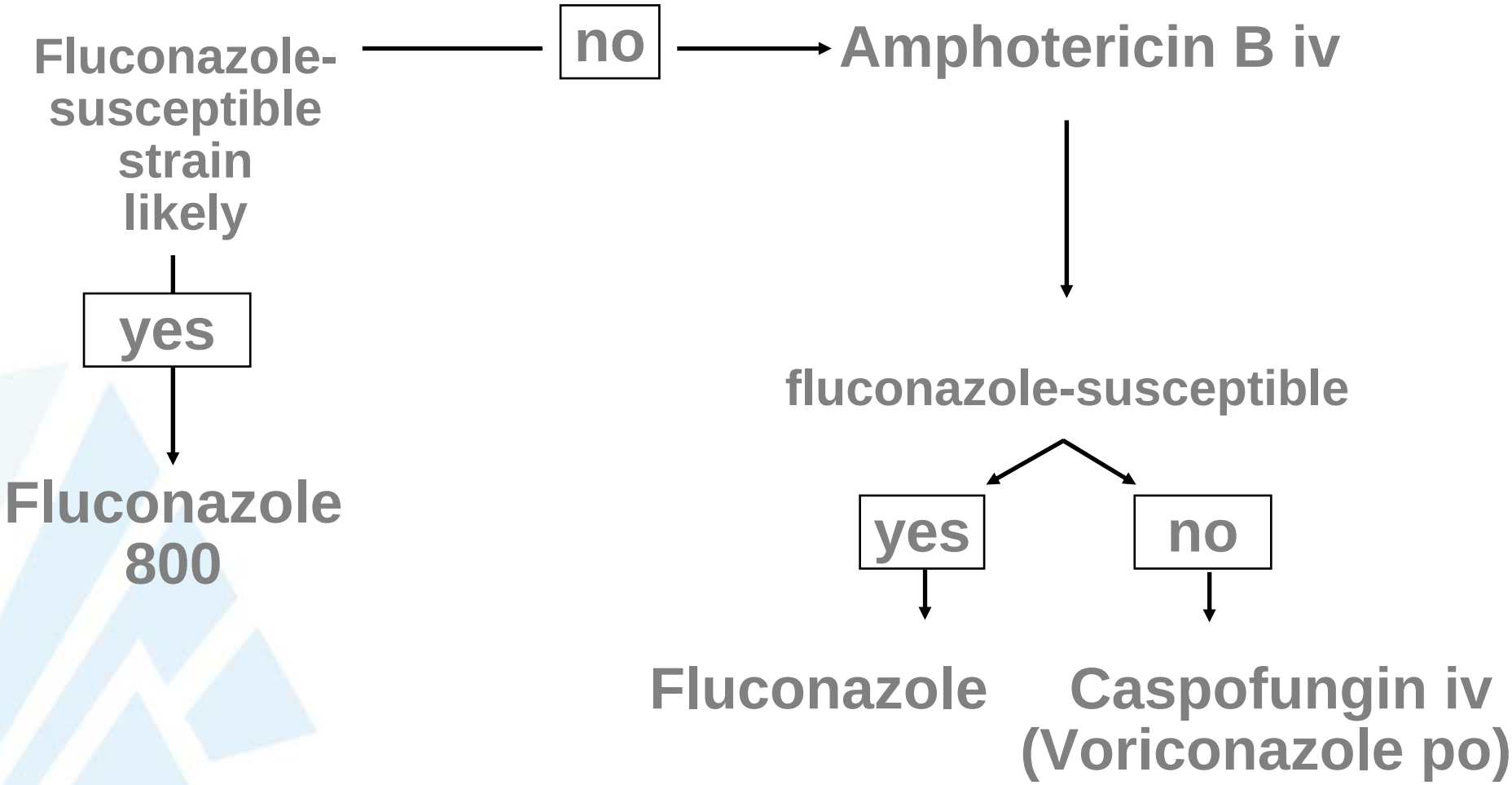
- Candidemia, non neutropenic, *C. glabrata*
  - Fluconazole only if susceptible
  - If on fluco and improving and S or SDD, continue fluco

Pappas, ICAAC 2007

How about Belgium?

- Reimbursement criteria for all but fluconazole and conventional ampho B
- “Yeast” in blood culture: choice between fluco and AmB only!
- Awaiting criteria for anidula (and mica)

How about Belgium?



How about Belgium?