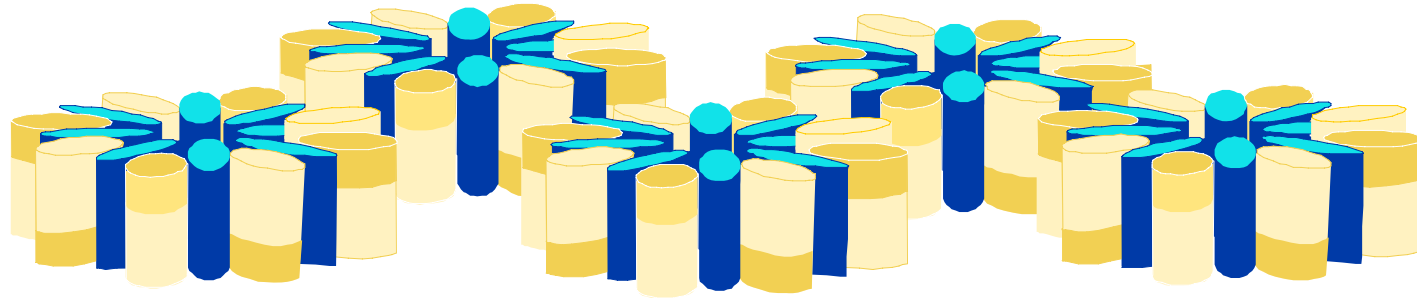


Amphotericin B Lipid Complex (Abelcet®)

ABLC: Structure and Activity



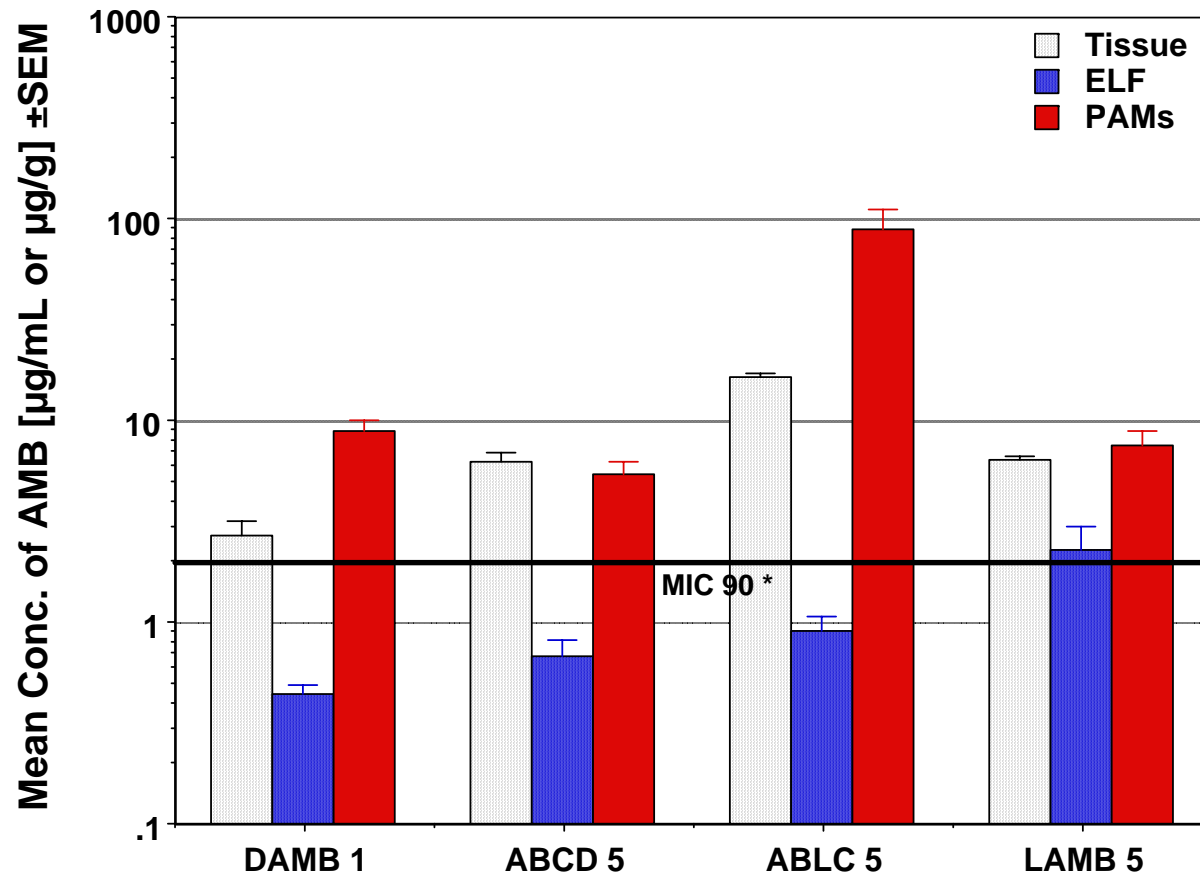
- **AMB : DMPC : DMPG lipid complex, 10:7:3 mol:mol**
- **ribbon-like lipid structures, 1.6-11 μm in diameter**
- **binds to ergosterol \rightarrow disturbance of cell membrane**
- **broad spectrum activity against most pathogenic fungi**

AmB Lipid Formulations: Plasma Pharmacokinetics

	D-AmB	ABCD	ABL	L-AMB
Std. dosage [mg AmB/kg]	1	5	5	5
Mean C _{max} [µg/mL]	2.9	3.1	1.7**	58
Mean AUC 0-24[µg/mL.h]	36	43*	14**	713
Mean V _d [L/kg]	1.1	4.3*	131	0.22
Mean Cl _t [L/h/kg]	0.028	0.117	0.476**	0.017

note that data were obtained in different (adult) patient populations and after different rates of infusion

AmB Lipid Formulations: Intrapulmonary disposition



ABLCL: Clinical Trials in Adults

- *Phase II*
 - Salvage therapy of invasive infections
 - Invasive aspergillosis
 - Invasive candidiasis
- *Phase III*
 - Invasive Candida-Infections
- *Phase IV*
 - Salvage therapy of invasive infections
 - Invasive aspergillosis, candidiasis, fusariosis, zygomycosis

Phase II Salvage Therapy

ABLCL: Phase II, Salvage Therapy

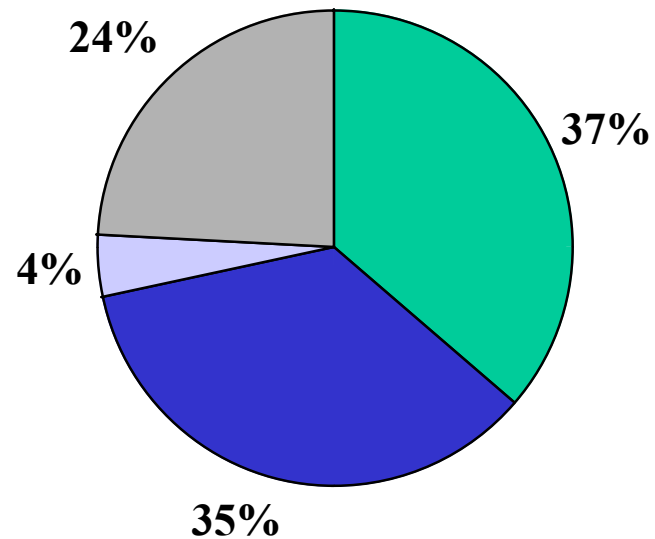
- Emergency use program, 556 patients invasive fungal infections refractory to / intolerant of DAMB
 - Mean age: 37.2 (21 d - 93 years)
 - Median daily dose: 4.91 mg/kg (r, <5 ->15)
 - Median duration: 22 days (r, 1-510)
- 291 mycologically confirmed cases (MITT)
- intolerance, 140; refractory IFI, 151
- Hem.malignancies, 27%; BMT, 20%, SOT, 19%

ABLCL

Phase II, Antifungal Efficacy

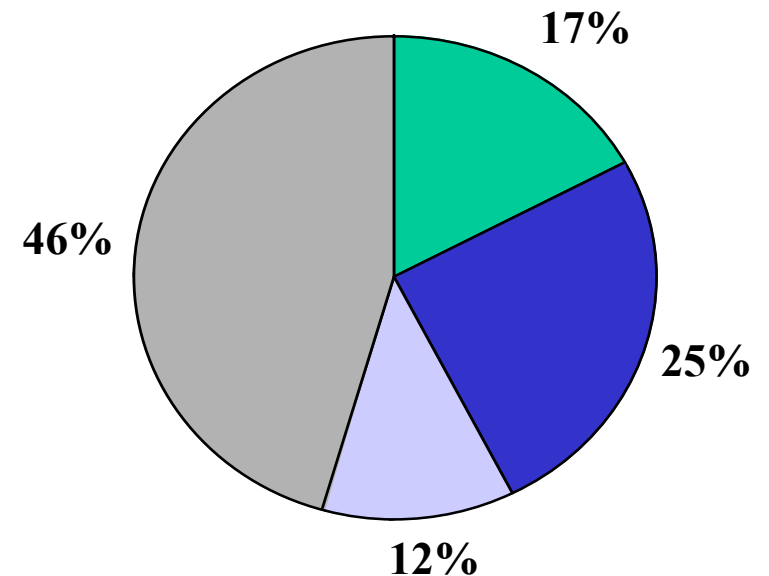


Inv. candidiasis (n=91):



CR/PR, 71%; ITT, 65%

Inv. aspergillosis (n=130):



CR/PR, 42%; ITT, 40%

ABLCL

Phase II, Safety & Tolerance



S-Cr stable/improved at EOT	396/555 (71 %)
S-Cr increased at EOT	132 /555 (24 %)
	- 63 \leq1.5 BL to $>$1.5 at EOT
	- 69 $>$1.5 BL to \geq120% at EOT
<hr/>	
Hypokalemia (any time)	24/518 (4.6 %)
Hypomagnesemia (any time)	65/369 (18 %)
<hr/>	
Bilirubin (\uparrow at EOT)	142/426 (33 %)
ALT (\uparrow at EOT)	87/348 (25 %)
<hr/>	
<i>DC due to AEs</i>	<i>49/556 (9 %)</i>

ABLCL: Phase II, Safety & Tolerance



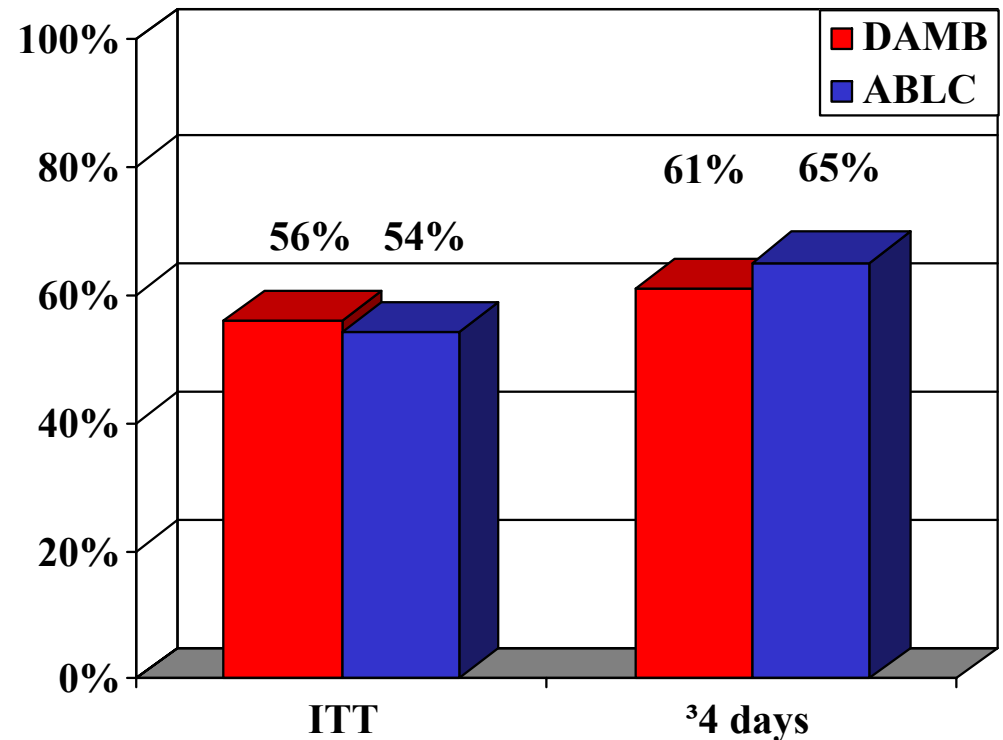
	Mean value		
	BL	EOT	P value
S-Cr [mg/dL]	2.11	2.10	0.8791
BUN [mg/dL]	54.8	60.1	0.0010
Bilirubin [mg/dL]	4.66	6.59	0.0001
AST [U/L]	67	147	0.2673
ALT [U/L]	73	76	0.8681
Alk Phos [U/L]	273	320	0.0015

Phase III Invasive Candidiasis

ABLCLC:

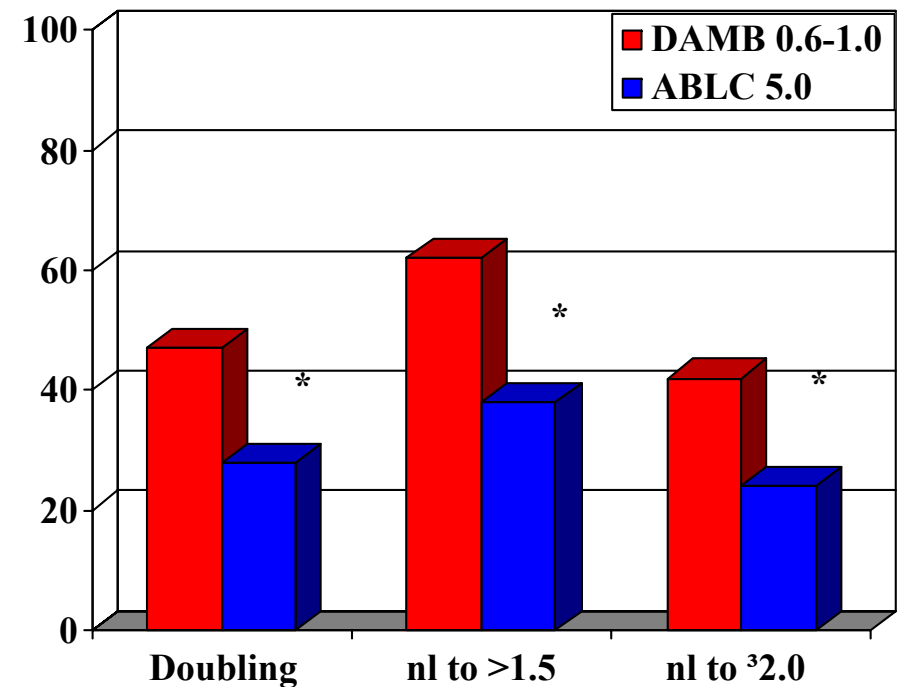
Phase III, Invasive Candidiasis

- Open label, 2:1 randomized multicenter trial in 231 pts ≥ 16 years
- ABLCLC 5 vs. DAMB 0.6-1.0
- Stratification according to ANC at baseline
- 194 pts evaluable for efficacy, 12% ANC < 500



ABLCL: Phase III, Safety & Tolerance

- Significant difference in nephrotoxicity
- No difference in LFT changes
- IRRs not separately assessed



- 8 vs. 19% AE-associated treatment discontinuations ($P=0.016$)

Phase IV CLEAR® Program

ABLC: Phase IV Collab. Exchange of Antifungal Research (CLEAR®)



- **Mission**

- Create a multicenter database for clinicians to share and exchange information on the pharmaco-epidemiology of ABLC for invasive fungal infections

- **Study design**

- Prospective enrollment of hospitalized patients receiving at least 4 doses of ABLC (n = 3514)
 - United States 1996-99, Canada 1997 to 2000
- Retrospective analyses
 - vast majority of cases were entered

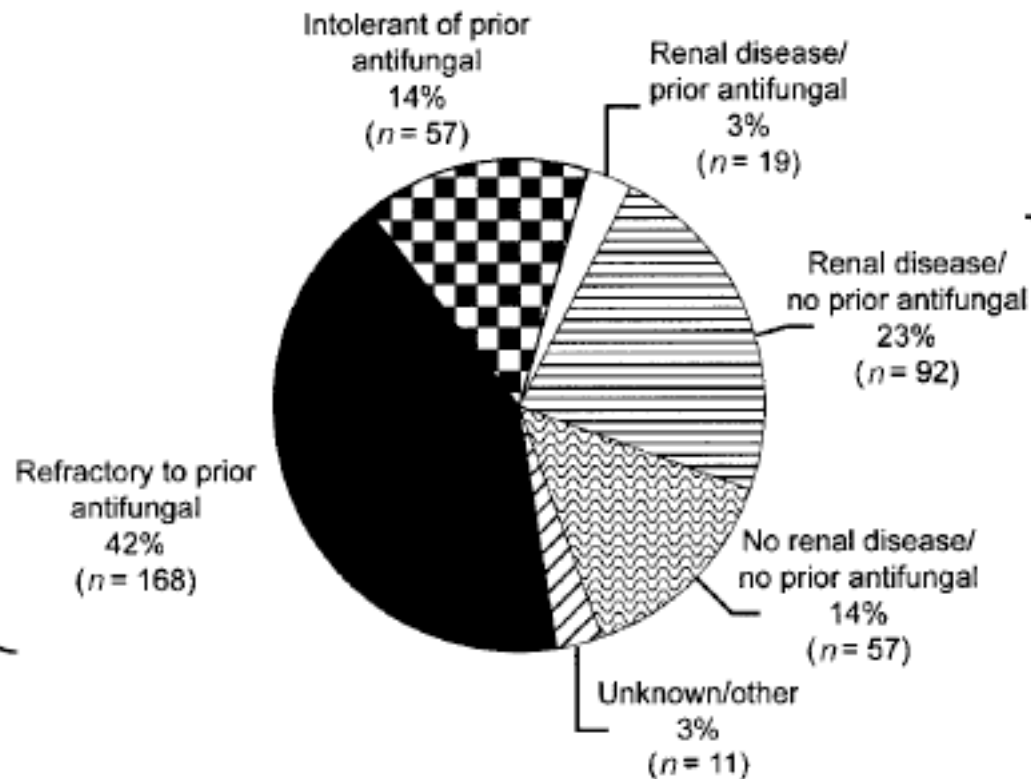
ABLCLC: CLEAR® Database, Aspergillosis



- 398 patients with 'proven' IA (investigator determined)
- 25% HSCT, 25% HMs, 27% SOT; 22% ANC <500 at BL
- 88% single site (lung, 71%) / 12% disseminated IA
- *A.fumigatus* (37%) > *A.flavus* (11%) > other
- Median dose of ABLCLC: 4.8 mg/kg/day (r, 0.2-10)
- Median duration of TX: 15 days (r, 1-274)

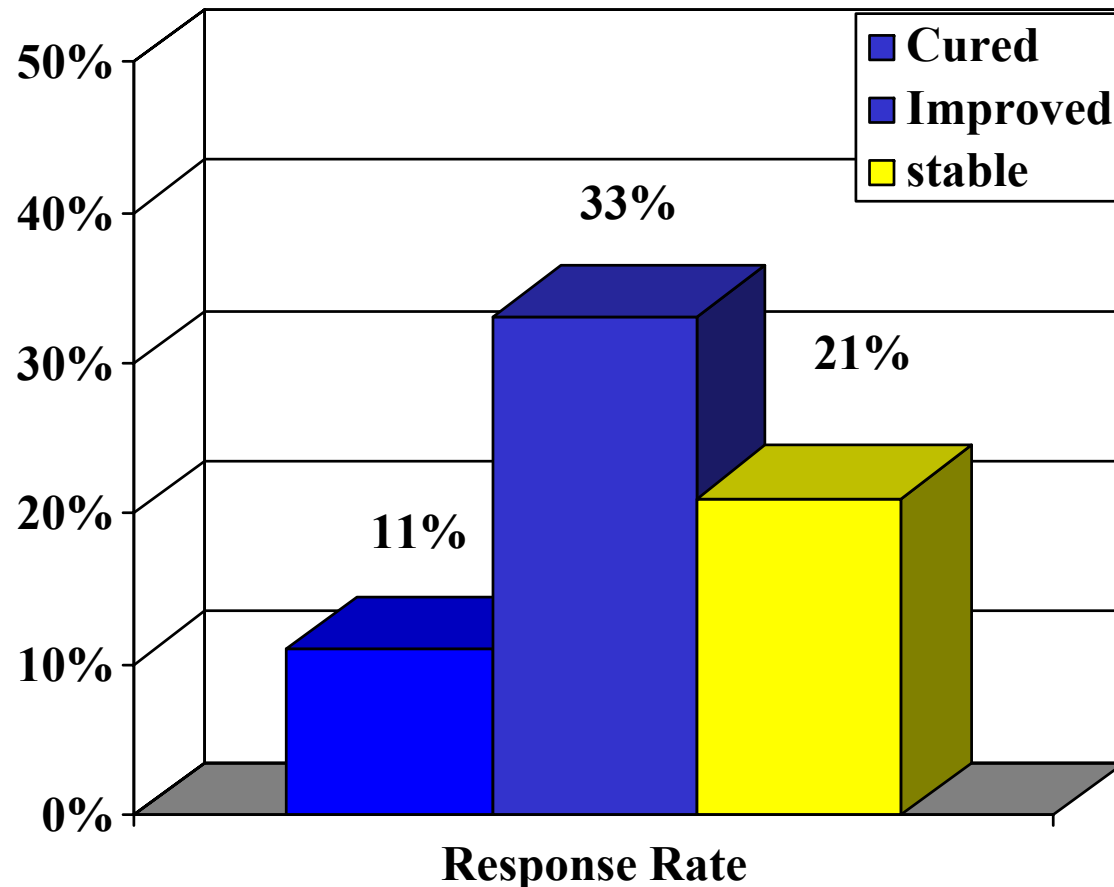
ABLCL CLEAR® Database, Aspergillosis

ABLCL as
second-line
therapy



ABLCL as
first-line
therapy

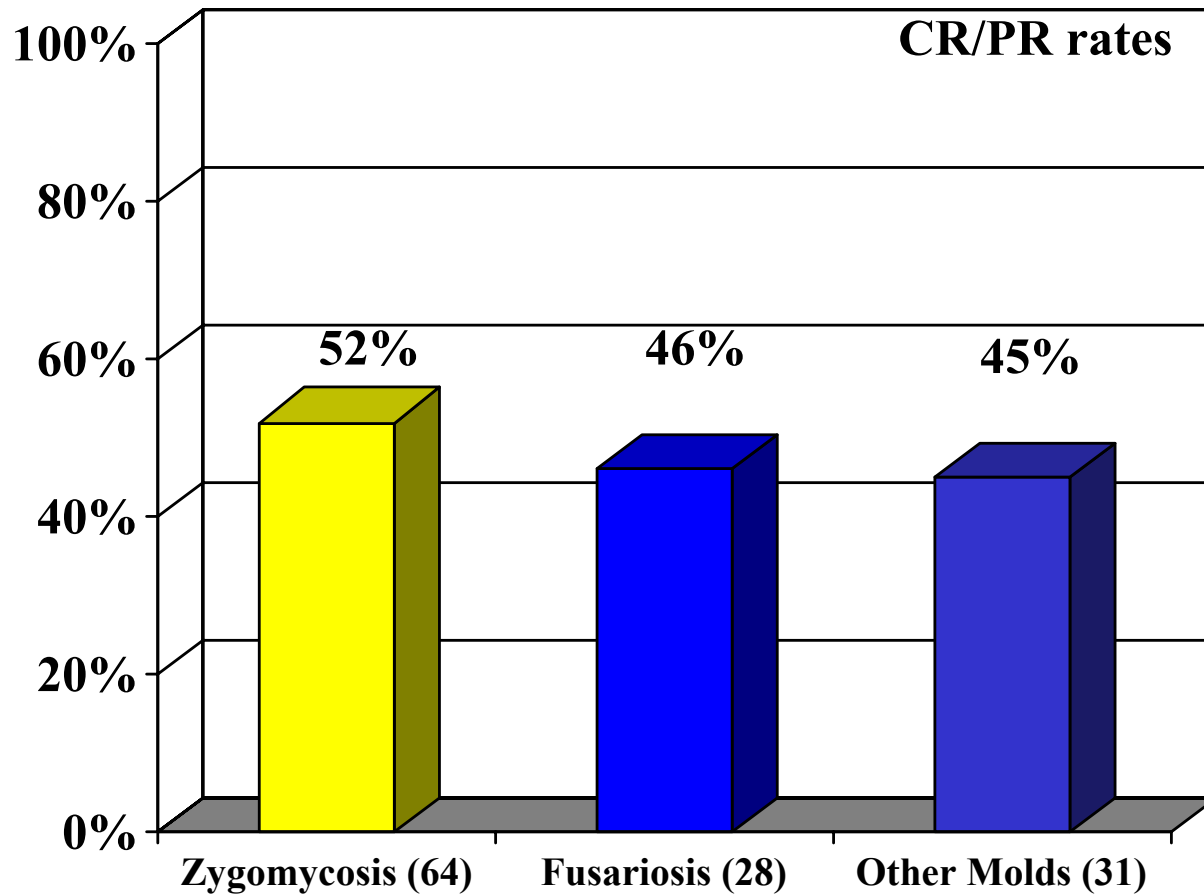
ABLCL: CLEAR® Database, Aspergillosis



368 eval. Patients

- 44% CR/PR
- 65% CR/PR/stable
- No differences first- vs. 2nd line

CLEAR® database, Non-*Aspergillus* opportun. Molds



Empirical Therapy / CLEAR®: Aspects of Safety

ABLCLC: Phase II, Empirical Therapy



- Randomized, double-blind multicenter study in 244 pts with refractory fever and neutropenia

	ABLCLC 5	L-AmB 5	L-AmB 3	P
<u>Day 1 IRR:</u>				
- chills/ rigors	79.5 %	23.5 %	18.8 %	< 0.001
- fever	57.7 %	19.8 %	23.5 %	< 0.001
<u>EOT Creatinine:</u>				
- x 2 base line	42.3 %	14.8 %	14.1 %	< 0.001
- mean change	1.0 mg/dl	0.4 mg/dl	0.5 mg/dl	< 0.001
<u>Hypoxia:</u>	20.5 %	6.2 %	7.1 %	< 0.05
<u>DC d/t toxicity:</u>	32.1 %	12.3 %	12.9 %	< 0.005

ABLCLC: CLEAR® Database, Renal Safety



- 3514 patients <1-97y with presumed/proven IFI
 - 56 % refractory / intolerant
 - 29% underlying renal disease
- 71 % allo HSCT / hematological malignancies
- Median daily dose: 4.4mg/kg (r, 0.2-10)
- Median duration: 12 days (r, 1-378)

ABLCLC: CLEAR® Database, Renal Safety



- *End of treatment:*

- Med. change in Cl-Cr: -3 ml/min (r, -119-118)
- Doubling of S-Cr: 13 %
- New dialysis: 3 %

- *Factors predictive for nephrotoxicity (x2 BL S-Cr or ↑ to ≥2.5 mg/dL) by logistic regression [OR / P]*

- | | | |
|---------------------------------|------|------------|
| - Concomitant nephrotoxic drugs | 1.26 | / 0.011 |
| - BL S-Cr <2 mg/dL | 1.71 | / <0.001 |
| - HSCT / HM | 1.18 | / 0.072 |
| - ABLCLC-dose > 5mg/kg | 1.20 | / 0.098 |

Pediatric Development

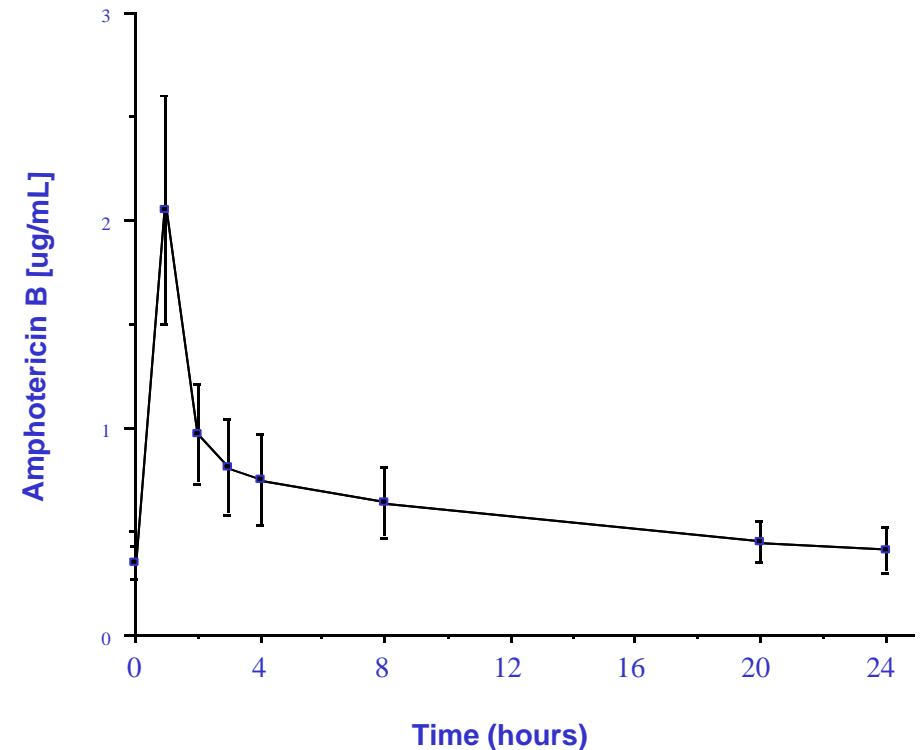
ABLCL: Clinical Trials, Pediatric Patients



- *Phase II*
 - Chronic-disseminated candidiasis
 - Inv. *Candida* infections in premature neonates
 - Salvage therapy of invasive infections
 - Invasive aspergillosis
 - Invasive candidiasis
- *Phase IV*
 - Salvage therapy of invasive infections (CLEAR®)
 - Invasive aspergillosis, -candidiasis

ABLCL: Pediatric Development

- No differences in disposition as compared to adults
- Dosage: 5 mg/kg QD over 2 h
- Licensed as 2nd line following DAMB
 - inv. candidiasis
 - inv. aspergillose



Conclusions

Conclusions

- Useful antifungal efficacy in treatment of IFI
- Large published datasets, including pediatric pts
- Acceptable safety and tolerance
 - Less nephrotoxic than conventional DAMB
 - IRR manageable by premedication
- ➡ Licensed for treatment of inv. candidiasis / inv. aspergillosis in pts refractory/intolerant to DAMB
- ➡ Dosage: 5mg/kg/d administered IV over 2 hours