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 → disturbance of cell membrane
- broad spectrum activity against most pathogenic fungi
**AmB Lipid Formulations: Plasma Pharmacokinetics**

<table>
<thead>
<tr>
<th></th>
<th>D-AmB</th>
<th>ABCD</th>
<th>ABLC</th>
<th>L-AMB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Std. dosage [mg AmB/kg]</td>
<td>1</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Mean Cmax [µg/mL]</td>
<td>2.9</td>
<td>3.1</td>
<td>1.7**</td>
<td>58</td>
</tr>
<tr>
<td>Mean AUC 0-24[µg/mL.h]</td>
<td>36</td>
<td>43*</td>
<td>14**</td>
<td>713</td>
</tr>
<tr>
<td>Mean Vd [L/kg]</td>
<td>1.1</td>
<td>4.3*</td>
<td>131</td>
<td>0.22</td>
</tr>
<tr>
<td>Mean Clt [L/h/kg]</td>
<td>0.028</td>
<td>0.117</td>
<td>0.476**</td>
<td>0.017</td>
</tr>
</tbody>
</table>

Note that data were obtained in different (adult) patient populations and after different rates of infusion.
AmB Lipid Formulations: Intrapulmonary disposition

Groll et al. submitted 05/06
ABLC:
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

Walsh 98; Anaissie ICAAC 95; Ito 05; Chandrasekar 05; 05; Perfect 05; Larkin 01
Phase II
Salvage Therapy
ABLC: 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%

Walsh et al. CID 98
ABLC: Phase II, Antifungal Efficacy

Inv. candidiasis (n=91):
- Complete: 35%
- Partial: 24%
- Stable: 4%
- Failure: 24%

CR/PR, 71%; ITT, 65%

Inv. aspergillosis (n=130):
- Complete: 46%
- Partial: 17%
- Stable: 12%
- Failure: 25%

CR/PR, 42%; ITT, 40%

05/06

Walsh et al., CID 98
**ABLC:**
**Phase II, Safety & Tolerance**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Count/Total</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>S-Cr stable/improved at EOT</td>
<td>396/555</td>
<td>71%</td>
</tr>
<tr>
<td>S-Cr increased at EOT</td>
<td>132/555</td>
<td>24%</td>
</tr>
<tr>
<td>Hypokalemia (any time)</td>
<td>24/518</td>
<td>4.6%</td>
</tr>
<tr>
<td>Hypomagnesemia (any time)</td>
<td>65/369</td>
<td>18%</td>
</tr>
<tr>
<td>Bilirubin (↑ at EOT)</td>
<td>142/426</td>
<td>33%</td>
</tr>
<tr>
<td>ALT (↑ at EOT)</td>
<td>87/348</td>
<td>25%</td>
</tr>
<tr>
<td><strong>DC due to AEs</strong></td>
<td><strong>49/556</strong></td>
<td><strong>9%</strong></td>
</tr>
</tbody>
</table>
### ABLC:
**Phase II, Safety & Tolerance**

<table>
<thead>
<tr>
<th>Mean value</th>
<th>BL</th>
<th>EOT</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>S-Cr [mg/dL]</td>
<td>2.11</td>
<td>2.10</td>
<td>0.8791</td>
</tr>
<tr>
<td>BUN [mg/dL]</td>
<td>54.8</td>
<td>60.1</td>
<td>0.0010</td>
</tr>
<tr>
<td>Bilirubin [mg/dL]</td>
<td>4.66</td>
<td>6.59</td>
<td>0.0001</td>
</tr>
<tr>
<td>AST [U/L]</td>
<td>67</td>
<td>147</td>
<td>0.2673</td>
</tr>
<tr>
<td>ALT [U/L]</td>
<td>73</td>
<td>76</td>
<td>0.8681</td>
</tr>
<tr>
<td>Alk Phos [U/L]</td>
<td>273</td>
<td>320</td>
<td>0.0015</td>
</tr>
</tbody>
</table>
Phase III
Invasive Candidiasis
ABLC: Phase III, Invasive Candidiasis

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

Graph: Comparison of DAMB and ABLC in ITT and 34 days.
ABLC:
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
ABLC: 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 ABLC: 4.8 mg/kg/day (r, 0.2-10)
- Median duration of TX: 15 days (r, 1-274)

Chandrasekar & Ito, CID 05
ABLC: CLEAR® Database, Aspergillosis
ABLC: 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

CR/PR rates

- Zygomycesis (64): 52%
- Fusariosis (28): 46%
- Other Molds (31): 45%
Empirical Therapy / CLEAR®: Aspects of Safety
ABLC: Phase II, Empirical Therapy

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

<table>
<thead>
<tr>
<th></th>
<th>ABLC 5</th>
<th>L-AmB 5</th>
<th>L-AmB 3</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Day 1 IRR:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- chills /rigors</td>
<td>79.5%</td>
<td>235%</td>
<td>188%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>- fever</td>
<td>57.7%</td>
<td>198%</td>
<td>235%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>EOT Creatinine:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- x 2 baseline</td>
<td>423%</td>
<td>148%</td>
<td>141%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>- mean change</td>
<td>1.0 mg/dl</td>
<td>0.4 mg/dl</td>
<td>0.5 mg/dl</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Hypoxia:</strong></td>
<td>20.5%</td>
<td>6.2%</td>
<td>7.1%</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td><strong>DC d/t toxicity:</strong></td>
<td>321%</td>
<td>123%</td>
<td>129%</td>
<td>&lt;0.005</td>
</tr>
</tbody>
</table>

Wingard et al., CID 99
ABLC:
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)
ABLC: 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** (\( \times 2 \) BL S-Cr or \( \uparrow \) to \( \geq 2.5 \) 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
  - ABLC-dose > 5mg/kg 1.20 / 0.098
Pediatric Development
ABLC: 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

Walsh 97; Walsh 99; Herbrecht 01; Wuerthwein 05; Wiley 05
ABLC: 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