Is combined antifungal therapy more efficient than single agent therapy?

Pro position

Nathan Keller Md PhD
The Chaim Sheba Medical Center
Israel
Disclaimer

- Advisory board - MSD, Pfizer, Neopharm
- Educational grants - Pfizer
Is there A Need

Are we satisfied with the current therapy?
Outcome of Invasive aspergillosis by years

![Graph showing the outcome of invasive aspergillosis by years. The graph plots the probability of survival against the number of days after the IA diagnosis. The years 1990-1992, 1993-1995, 1996-1998, 1999-2001, and 2002-2004 are differentiated by different line styles and colors.]
Kaplan-Meier survival curves for patients with rhino-orbital-cerebral mucormycosis treated with various antifungal agents.
Yes there is a need!!!

!!!No we are not satisfied
I will not discuss today uncomplicated clinical situation
I will discuss severe conditions such as Zygomycosis, invasive aspergiliosis etc.
History lesson

- Combinations can be GOOD
  - *Enterococcus*: PCN (or amp or vanc) + gent
    - Good in endocarditis. But, not clearly so at other sites
- Combinations can be BAD
  - PCN + chloramphenicol in pneumococcal meningitis
    - Adding chloro decreased survival from 79 to 21%
- Assessing all this in vitro is TRICKY
  - Technical: *Enterococcus*, PCN, & gent
    - Checkerboard is not reliable—must use time-kill (impractical in clinical setting)
  - Some interactions (e.g., metabolic) not seen
Advantages of combination antifungal therapy

- Synergy
- Broader therapy
- Decreased resistance
- Pharmacokinetic enhancement
- Better tolerance with lower doses
What is the proper way to test this question?

What makes this question a difficult one?
Combination Strategies Unique to Fungal Infections

- Overall Mortality Rates Very High
- Toxicity of Antifungals is Significant
- Fungal Diseases Relatively Rare
- Drug Costs High
- Superiority Trials for Efficacy Preferred
Unique Aspects of Combination Treatment for Fungal Infections

- Surrogate Endpoints Rare/non-existent
- Multiple Companies Needed for Studies
- Historical Trials Problematic
- Relatively Few Agency Approved Drugs
- Standard of Care May Be Combinations
Randomised Controlled studies will never be performed
Level of evidence of IDSA guidelines

Table. Distribution of Individual Recommendations From Current Infectious Diseases Society of America Guidelines According to Strength of Recommendation and Quality of Evidence

<table>
<thead>
<tr>
<th>Strength of Recommendation</th>
<th>Level I</th>
<th>Level II</th>
<th>Level III</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level A</td>
<td>414 (23)</td>
<td>715 (40)</td>
<td>667 (37)</td>
<td>1796 (100)</td>
</tr>
<tr>
<td>Level B</td>
<td>143 (8)</td>
<td>544 (30)</td>
<td>1132 (62)</td>
<td>1819 (100)</td>
</tr>
<tr>
<td>Level C</td>
<td>24 (4)</td>
<td>48 (8)</td>
<td>531 (88)</td>
<td>603 (100)</td>
</tr>
<tr>
<td>Total</td>
<td>581 (14)</td>
<td>1307 (31)</td>
<td>2330 (55)</td>
<td>4218 (100)</td>
</tr>
</tbody>
</table>

A1 = 10%  
C = 55%

Dong Heun Lee, MD; Ole Vielemeyer, MD  Arch Intern Med. 2011;171(1):18-22
Where are we going?

Expert Opinion
Combination Therapy Rationale

- Widened spectrum and potency
- More rapid antifungal effect
- Additive or synergistic efficacy effects
- Lowered dosing or less toxicity
- Reduce risk of emerging resistance
Combination Therapy Rationale Cont.

- Historic poor outcomes with monotherapy
- Increased penetration / transport
- Inhibit different stages of the same biochemical pathway
- Simultaneous inhibition of different fungal targets
- Creation of a fungicidal combination
Current targets of therapy for
3 possible mechanisms by which addition of an echinocandin may improve the efficacy of polyene therapy for mucormycosis

- Disruption of β glucan cross-linking of the cell wall, leading to enhanced polyene delivery to the cell membrane;
- Altered virulence of the fungus, either by stunting filamentation or altering cell wall content
- Enhanced host response to the fungus. Investigation into the mechanism of action of echinocandin combination therapy is ongoing.
For an expert opinion we need

- In vitro data
- Animal model data
- Human data
In vitro data
Combinations of antifungal agents against C. albicans biofilms in vitro

- biofilms in 96-well plates
- checkerboard combinations:
  - sessile cells: SMIC80
  - planktonic cells: MIC: NCCLS
- CAS+AMB: additive
- FLU+AMB: no alteration of ABM activity
- FLU+CAS: antagonism (not under planktonic conditions)

Conclusion:
- AMB+CAS: increased activity
- FLU inhibited CAS activity

*Bachman et al. 42nd ICAAC, M-1813*
Experimental - (aspergilus )
Voriconazole + Caspofungin

- In Vitro
  - 48 isolates, Synergy (87.5%) of interactions (FICI < 1.0)


Ravuconazole + Micafungin Hyphal Damage

- The spherical chlamydoconidial structures are evidence of the effect of echinocandins
- The focal hyphal disintegration and disruption are compatible with the effects of triazoles
- Original magnification ×630; Insert, ×1000; Scale bar 20 um

So there are In vitro evidence for combination therapy!!!
Animal model
Experimental Aspergillus Ravuconazole + Micafungin

- Neutropenic rabbit model
  - Survival
    - Micafungin monotherapy (0/8)
    - Ravuconazole monotherapy (2/8)
    - Micafungin + Ravuconazole (9/12)
  - Fungal burden, GM assay, Pulmonary injury, Pulmonary infiltrates all less in the combination

**Experimental Aspergillus**

**Voriconazole + Caspofungin**

*In Vivo:* Neutropenic guinea pig model

- Mortality (0/12 animals) and survival time (8 days) SAME in EACH of these arms:
  - VCZ 5mg/kg/d
  - CAS (1 mg/kg/d) + VCZ
  - CAS (2.5 mg/kg/d) + VCZ

- Fungal burden (CFU) with combination better than untreated controls only

- *Number of organs with positive cultures with combination better than monotherapy*

Aspergillus - animal models

• Neutropenic rabbit IPA model
• Micafungin + ravuconazole
• Pharmacokinetics verified to ensure drug exposure similar to humans
• Improved survival
  combo 9/12 vs Mica 0/8 vs RVC 2/8 vs controls 0/8 \( p \leq 0.001 \)
  • Reduced
    - residual fungal burden \( p \leq 0.05 \)
    - GM antigenaemia \( p \leq 0.01 \)
    - Infection mediated pulmonary injury \( p \leq 0.05 \)
    - no. of pulmonary infiltrates on CT \( p \leq 0.001 \)
• No toxicity
• Synergy confirmed \textit{in vitro}
So combinations are advantageous in animal models
Human studies
Reports on clinical combination therapy

- Caspofungin + L-AmB salvage after previous L-AmB (n=48)
  - Overall response rate 42%; Response in progressive IA 18%

- Micafungin + existing antifungal in 85 BMT pts
  - 39% (28%) complete/partial response
Combination antifungal therapy for invasive aspergillosis

- 47 patients with proven/probable IA from 1997-2001
- Patients experienced failure of initial therapy with AmB formulations
- Received either voriconazole (n=31) or voriconazole + caspofungin (n=16) as salvage therapy
- Voriconazole + Caspofungin with improved 3-month survival rate compared to voriconazole monotherapy (HR 0.42; 95% CI 0.17-1.1; p=0.048)
- Multivariate model, combination with reduced mortality (HR 0.28; 95% CI 0.28-0.92; p=0.01)

Upfront Combination Therapy for IA

- Retrospective single center cohort review of consecutive patients with IA and an underlying hematologic malignancy (Jan 98 – July 03)
- Proven (n=17) / Probable (n=17) / Possible (n=11) by EORTC/MSG
- Data presented below for Proven / Probable cases only

<table>
<thead>
<tr>
<th></th>
<th>ALL (n=34)</th>
<th>Combo (n=10)</th>
<th>Mono (n=24)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 wk Survival</td>
<td>53%</td>
<td>50%</td>
<td>54%</td>
<td>0.82</td>
</tr>
<tr>
<td>Median Survival (d)</td>
<td>110</td>
<td>102</td>
<td>115</td>
<td>---</td>
</tr>
<tr>
<td>CR/PR</td>
<td>41%</td>
<td>50%</td>
<td>37.5%</td>
<td>0.5</td>
</tr>
<tr>
<td>Stable</td>
<td>5.9%</td>
<td>0%</td>
<td>8.3%</td>
<td>--</td>
</tr>
<tr>
<td>Failure</td>
<td>53%</td>
<td>50%</td>
<td>54%</td>
<td>0.86</td>
</tr>
</tbody>
</table>

- No differences in survival between primary therapy with mono vs. combo

Combination antifungals for treatment of pulmonary invasive aspergillosis refractory to AMB in leukaemia patients

- Combination Tx started 8 d after diagnosis
- Definite IA: 3 pts
- Probable IA: 3 pts
- CAS+L-AMB: 4 pts
- CAS+VORI: 2 pts
- Mean duration: 62 d (42-107)
- 3 pts died: none attributed to IA
- No toxicity seen

Conclusion: "combination therapy useful salvage therapy for IA refractory to AMB"
Caspofungin + L-AmB as primary or salvage therapy of IA

- 48 pts 23 prov/prob 25 poss
- 65% salvage Rx
- 35% primary Rx
- 50% BMT
- 63% neutropenic
- Prior L-AmB 9d (7-35)
- Combination Rx 20d (7-180)

- Overall response 42 prov/prob 22 poss 60
- Prior L-AmB response 35 prov/prob 18
- Primary therapy 53 prov/prob 33
- Overall mortality 35
- 5 pts responded while neutropenic
- Mild-mod renal impairment in 15%
Kaplan-Meier survival curves for patients with rhino-orbital-cerebral mucormycosis treated with various antifungal agents.


© 2008 by the Infectious Diseases Society of America
### TABLE 3. Summary of key findings reported in studies of *C. neoformans* with combinations of clinically relevant antifungal agents

<table>
<thead>
<tr>
<th>Combination</th>
<th>Settings studied</th>
<th>General findings</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>5FC + AmB</strong></td>
<td>In vitro (60, 65, 74, 78, 89, 92, 126, 140, 156, 158)</td>
<td>Indifference (63, 74, 78, 89, 140, 156, 158) synergy (49, 126), antagonism with 5FC-resistant strain (89)</td>
<td>AmB reduces development of resistance to 5FC; 5FC-resistant strains have been used in numerous studies (80, 126, 158) and produce various results. Survival (27) or reduction in tissue burden (150) not necessarily better than results with AmB alone (60); combination more effective than AmB and 5FC alone against 5FC-resistant strains (158).</td>
</tr>
<tr>
<td></td>
<td>Mice (16, 27, 60, 80, 158)</td>
<td>Improved survival (16, 27, 158), Reduced tissue burden (16, 158)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Rabbits (150)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Humans (24, 42, 43, 55, 103, 144, 213)</td>
<td>Similar (213) or improved (24, 171) clinical success overall, improved sterilization of CSF (24, 213)</td>
<td>Survival (27) or reduction in tissue burden (150) not necessarily better than results with AmB alone (60); combination more effective than AmB and 5FC alone against 5FC-resistant strains (158).</td>
</tr>
<tr>
<td><strong>5FC + triazoles</strong></td>
<td>In vitro</td>
<td>FLC: synergy (138), KTC: indifference (31, 89), ITC: PSC: indifference or synergy (12, 14)</td>
<td>Synergy in 62% of 50 strains studied for FLU-5FC (138); various doses may be necessary to achieve greater effect; addition of 5FC helped prevent emergence of 5FC-resistant mutants.</td>
</tr>
<tr>
<td></td>
<td>FLC (5, 138, 140), KTC (31, 140), ITC (12), PSC (14)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Animal studies</td>
<td>Improved (3, 50, 61, 157), similar (14, 50, 60, 212), or worse (89) survival</td>
<td>Combination associated with better survival than monotherapy and was consistent over a range of doses (3); effects more pronounced at lower doses (101), and single agents were very effective at higher doses; 5FC + KTC rarely cleared tissues better than either agent alone (120); hamsters with combination did worse than with ITC alone (89); ITC + 5FC performed similarly to ITC + AmB and better than ITC or 5FC monotherapy in guinea pigs (212); with 10 days of treatment of mice, combination prolonged survival more than either agent alone but not when treatment was limited to 5 days (157). FSC combination not better than monotherapy in terms of survival but better than monotherapy in reducing fungal counts in brain tissue (14)</td>
</tr>
<tr>
<td></td>
<td>FLC: mice (3, 60, 61, 101, 120, 157)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>KTC: mice (50, 78, 158) and rabbits (150)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>ITC: mice (157), hamsters (89), and guinea pigs (212)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>PSC: mice (14)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Humans</td>
<td>Good clinical success (48, 102, 193, 225), Increased survival (124)</td>
<td>63% success rate in cryptococcal meningitis (95% confidence interval, 48-82% (102) improved survival (32%) versus FLC alone (124) at 6 months in AIDS-associated cryptococcal meningitis (124).</td>
</tr>
<tr>
<td></td>
<td>FLC (48, 102, 124, 193, 225)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>AmB + triazoles</strong></td>
<td>In vitro</td>
<td>Indifference (13, 78, 140)</td>
<td>FLC: indifference in 10/15 strains tested, indifference in 4/15, and synergy in 1/15 with MCCLS methods (13); indifference among 3 strains using an inoculum of 104 CFU/ml on yeast nitrogen base broth and response surface plots (74); KTC: no antagonism observed (78, 140, 150); synergy reported with one strain in two studies using nonstandard methodologies (140, 161); ITC: 14/15 strains indifferent; 1/15 synergistic (13); FLC: 8/15 strains indifferent; 3/15 synergistic; 2/15 indifferent in one study (13).</td>
</tr>
<tr>
<td></td>
<td>FLC (13, 74), KTC (78, 140, 150, 161), ITC (12), PSC (13)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Animal models</td>
<td>FLC/KTC: improved survival compared to results with azole (2, 13, 78, 158) and/or AmB (2, 158)</td>
<td>FLC: addition of AmB to FLC had dramatic impact on yeast burden in broth cultures (1), but survival with AmB was 100%; effects on survival were greatest at high inoculums of azole-AMB (2, 158); improved survival at lower doses of ITC = AmB, but survival was worse when higher doses were used (157). FLC preexposure did not reduce subsequent AmB activity (13).</td>
</tr>
<tr>
<td></td>
<td>FLC: mice (2, 13)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>KTC: mice (50, 78, 158) and rabbits (150)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>ITC: mice (157) and guinea pigs (212)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Humans—case report (47)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Caspofungin or anidulafungin + AmB</strong></td>
<td>In vitro (71)</td>
<td>Synergy</td>
<td>Used higher levels of caspofungin than would be used for humans.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Caspofungin or anidulafungin + FLC</strong></td>
<td>In vitro (71, 169)</td>
<td>Indifference (71, 169) or synergy (71)</td>
<td>One study showed that echinocandins were no better than FLC monotherapy (169); no antagonism (71, 169).</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>ITR + FLC</strong></td>
<td>Guinea pigs (212)</td>
<td>Reduced tissue burden</td>
<td>Survival was 100% in all treatment groups; improved sterilization of tissues compared to FLC but not ITC.</td>
</tr>
</tbody>
</table>

---

*AmB*, amphotericin B; CLT, clotrimazole; FLC, fluconazole; 5FC, fluocytosine; KTC, ketoconazole; ITC, itraconazole; PSC, posaconazole; RVC, ravuconazole; SFC, saquinavir; TFC, trifluridine; VRC, voriconazole.

---

*Larson et al., Abstr. 9th Int. Conf. Oggocococc Dis., 2002.*
Summary: Relevance of Combination Therapy

- Majority of existing studies are anecdotal, retrospective, and or non-comparative
  - Prospective, double blind studies are exceedingly problematic in design issues and feasibility
  - Prospective, double blind, trials will be forthcoming but highly restricted in number
  - Weight of the evidence is in favor of combination therapy in seriously ill patients with invasive fungal infections
- Until studies are completed, use combination therapy in serious cases
- Tolerance of the patient for the combination needs to be carefully monitored to justify the use.
Thank you