Antifungal drug resistance: the impact in clinical management

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• **Microbiological R**

Nonsusceptibility of a fungus to an antifungal agent by in vitro susceptibility testing, in which the MIC of the drug exceeds the susceptibility breakpoint for that organism

- **Primary R (intrinsic):**
  i.e.: *Candida krusei* to FLU, *Cryptococcus neoformans* to echinocandins

- **Secondary R (acquired):**
  i.e.: development of FLU R in *Candida albicans* or *Cryptococcus neoformans*

- Clinical R can be attributed to a combination of factors related to host, the antifungal agent, or the pathogen

• **Clinical R**

Failure to eradicate a fungal infection despite the administration of an antifungal agent with in vitro activity against the organism

Antifungal Susceptibility Testing

- Technical differences:
  - medium, inoculum size, time of incubation, readings

- CLSI breakpoints (µg/ml):
  - **FLU**: S ≤ 8, R ≥ 64
  - **ITRA**: S ≤ 0.125, R > 1
  - **VORI**: S ≤ 1, R > 4
  - **ECHINOCANDINS**: “NS” ≤ 2 µ/ml

- EUCAST breakpoints (µg/ml):
  - **FLU**: S ≤ 2, R > 4
  - **VORI**: S ≤ 0.125, R > 0.125

- Commercial methods are available that display good correlation with the methods of reference such as E-test, Sensititre and Vitek2

**In Vitro / In Vivo Correlation**

- The discordance between in vitro and in vivo data is illustrated by the “60-90 rule”, which maintains that infections due to S strains respond to appropriate therapy in ~90% of cases, while infections due to R strains respond in ~60% of cases.

- Although AST predicts treatment failure in patients with HIV infection and OPC, no such correlation has been replicated in other settings.

- MIC levels are not always the most optimal measure of R (i.e.: MECs for echinocandins vs molds).

- Clinicians are still faced with the challenge of how to interpret the results of in vitro AST.

- MIC values do not always directly associate with response to antifungal therapy.

- Variable results according to the type of patient.

- Discrepancy between yeast and mold infections.

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Resistance to Azoles

- 256882 isolates of *Candida* spp. tested for FLU
- 197619 isolates of *Candida* spp. tested for VORI
- 30% of FLU-R isolates remained S to VORI
- An increase in FLU R over time was seen with *C. parapsilosis*, *C. guilliermondii*, *C. lusitaniae*, and *C. pelliculosa*

Susceptibility to one azole predicts susceptibility to all?

- There is a good correlation
- There is enough differences that testing each agent is worthwhile
- Especially vori and posa
  - As FLU MICs rise, so do these but
  - Not always so much and not always to “untreatable” levels
  - E.g., vori data suggests at least some activity vs. *C. krusei* - 7/10 (70%) salvage response rate

Geographic variation in the frequency of isolation and fluconazole and voriconazole susceptibilities of *Candida glabrata*: ARTEMIS DISK

Clinical breakpoints have not been established for mold testing

- Proposed for *Aspergillus* spp:
  - ITRA and VORI R > 2.0 μg/ml
  - POSA R > 0.5 μg/ml

- Although ECVs do not predict therapy outcome, they may aid in detection of azole resistance (non-WT MIC)

- Cross-resistance between azole drugs depends on specific mutations in cyp51A:
  1. gly 54 ITRA/POSA
  2. meth 220 ITRA/POSA/VORI
  3. leu 98 + duplication 34.bp promoter cyp51A ITRA/POSA/VORI

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The burden of echinocandin resistance is still poorly appreciated.

Recent reports of R in patients with *C. albicans*, *C. krusei*, *C. parapsilosis*, *C. glabrata* infections.

Among the *Candida* spp., *C. parapsilosis* and *C. guilliermondii* isolates have higher MIC values than do *C. albicans* isolates.

Comparable levels of inhibitory activity of the three agents vs *Aspergillus* spp.

Clinical studies showed no correlation between *Candida* species and outcome.

A relationship between MIC for echinocandins and treatment outcome was not seen for patients with either esophageal candidiasis or invasive candidiasis.

Experimental data show that the overall CFU reduction for *C. guilliermondii* and *C. parapsilosis* is approximately 100-fold less than that for *C. albicans*.

Resistance to Polyenes

- Identification of polyene-resistant isolates has been difficult to reproduce.
- Molds are more likely than yeasts to have reduced susceptibility to polyenes:
  - 1° R- *A. terreus*,
  - 2° R- *A. flavus, A. fumigatus; Scedosporium apiospermum, S. prolificans, and Fusarium spp.*
- Among the *Candida* spp., *C. krusei* and *C. glabrata* have increasing MIC values;
  - 1° R- *C. lusitaniae*

# Invasive candidiasis

<table>
<thead>
<tr>
<th>Drug / Comparator</th>
<th>response rate (%)</th>
<th>N° of patients</th>
<th>reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAS / dAMB</td>
<td>80.7 / 64.9</td>
<td>239</td>
<td><em>N. Engl. Med.</em>, 2002, 347:2020-9</td>
</tr>
<tr>
<td>MICA / L-AMB</td>
<td>89.6 / 89.5</td>
<td>531</td>
<td><em>Lancet</em>, 2007, 369:1519-27</td>
</tr>
<tr>
<td>ANIDULA / FLU</td>
<td>75.6 / 60.2</td>
<td>245</td>
<td><em>N. Engl. Med.</em>, 2007, 356:2472-82</td>
</tr>
</tbody>
</table>
## Invasive mold infections

<table>
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<tr>
<th>Drug / Comparator</th>
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</table>
When primary antifungal therapy fails

- Antifungal therapy failure is still a substantial clinical problem
- When this occurs, the clinician is tempted to attribute therapeutic failure to specific drug resistance and then to change therapy or add another antifungal drug to the regimen
- Other factors may play an even greater role in antifungal therapy failure

<table>
<thead>
<tr>
<th>Host factors</th>
<th>Wrong diagnosis</th>
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</thead>
<tbody>
<tr>
<td><em>(severity of illness; persistence of immunodeficiency – i.e: neutropenia or use of corticosetoids)</em></td>
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<tr>
<td>Mixed infection</td>
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<tr>
<td>Low concentration of the drug at the site of infection <em>(PK/PD; biofilms; poor vascular supply)</em></td>
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<td>Drug toxicities <em>(direct and with drug interactions)</em></td>
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<tr>
<td>Misdiagnosis of failure</td>
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<tr>
<th>Patient / type of infection</th>
<th>Factors associated with poor prognosis</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonneutropenic</td>
<td>Older age, longer ICU stay, Retention of central line</td>
<td>Luzzati et al., EJCMID, 2000, 19:602-7</td>
</tr>
<tr>
<td><strong>Candidemia</strong></td>
<td>Neutropenia, Corticosteroid therapy, Retention of central line, Higher Apache II score</td>
<td>Viudes et al., EJCMID, 2002, 21:767-74</td>
</tr>
<tr>
<td>Mixed population</td>
<td>Higher Apache III score, inadequate initial therapy</td>
<td>Bassetti et al., DMID, 2007, 58:325-31</td>
</tr>
<tr>
<td><strong>Candidemia</strong></td>
<td>Prolonged steroid treatment, uncontrolled GVH</td>
<td>Ribaud et al., Clin Infect. Dis., 1999, 28:322-30</td>
</tr>
<tr>
<td><strong>Aspergillosis</strong></td>
<td>Neutropenia, allogenic SCT</td>
<td>Subirà et al., Hematologica, 2002, 87:528-34</td>
</tr>
<tr>
<td>HSCT</td>
<td>Disseminated IA, Severe neutropenia (&lt;120/mmc), prolonged steroid treatment, uncontrolled GVH</td>
<td>Cordonier et al., Clin Infect. Dis., 2006, 42:955-63</td>
</tr>
</tbody>
</table>
CONCLUSIONS

- Antifungal drug resistance is prominent feature in the management of invasive mycoses
- Its epidemiological characteristics continue to evolve
- A principal factor in patients with serious underlying diseases is clinical resistance

The surveillance should be carried out using the reference procedures and taking into account the breakpoints established by the expert committees of the CLSI and EUCAST.
Thank you for your attention