The antifungal formulary

What are we missing?

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“If many drugs are used for a disease, none are sufficient”

Sir William Osler, M.D.
1849 – 1919
The antifungal pipeline

past, present and future?

On the horizon?
- CD-101, rezafungin (Cidara)
- SCY-078, ibrexafungerp (Scynexis)
- VT-1161 (Viamet)
- VT-1129 (Viamet)
- VT-1598 (Viamet)
- F901318 (F2G)
- APX001 (Amplex)
- VL-2397 (Vical)
What are we missing?

- Novel mechanism of action
- Emerging resistance
MDR Candida auris

- Simultaneously emerged on three continents
- Can colonize patient skin *for months*
- Can survive on hospital surfaces *for months*
- Associated with hospital outbreaks similar to MRSA or *Acinetobacter* spp. (*horizontal patient transmission*)
- Frequently misidentified by standard microbiological methods
- Frequently resistant to multiple antifungal classes... and increasingly echinocandins

Countries from which *Candida auris* cases have been reported, as of August 31, 2018

In some hospitals *C. auris* has accounted for up to 40% of isolates

Source: CDC
Jeffery-Smith A, et al.. Clin Microbiol Rev 2018; 31
MDR Aspergillus fumigatus

Shaded areas showing countries that have reported TR$_{34}$/L98H and TR$_{46}$/Y121F/T289A resistance mechanism

Image: P. Verweij, Radbound Univ

Aspergillus fumigatus isolate from Italy that only grows in the presence of voriconazole

5 year, multicenter, retrospective study in Netherlands n=196 patients (2011-2015)

21% higher mortality at day +42
Not just *Aspergillus fumigatus*

65 y/o female with AML, fever, severe respiratory difficulty, ANC 250

BAL grew H1N1 influenzae, *A. terreus*, GM 3.1

<table>
<thead>
<tr>
<th>Antifungal</th>
<th>MIC</th>
<th>EUCAST Interp.</th>
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</thead>
<tbody>
<tr>
<td>Amphotericin B</td>
<td>4 mg/L</td>
<td>R</td>
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<tr>
<td>Anidulafungin</td>
<td>&gt;4 mg/L</td>
<td>R</td>
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<tr>
<td>Caspofungin</td>
<td>&gt;4 mg/L</td>
<td>R</td>
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<tr>
<td>Micafungin</td>
<td>&gt;4 mg/L</td>
<td>R</td>
</tr>
<tr>
<td>Isavuconazole</td>
<td>2 mg/L</td>
<td>R</td>
</tr>
<tr>
<td>Voriconazole</td>
<td>1 mg/L</td>
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</tr>
<tr>
<td>Posaconazole</td>
<td>0.06</td>
<td>S</td>
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</tbody>
</table>

Case courtesy of Marta Stanzani, M.D., Ph.D:
Limited treatment options, high mortality

- Resistant *Aspergillus*
- *Fusarium* spp.
- Mucorales
- *Scedosporium apiospermum*
  *Lomentospora prolificans*
What are we missing?

- Novel mechanism of action
- Emerging resistance
- Adequate PK
DALI Study
Defining antibiotic levels in the ICU

• Prospective, multicentre PK point-prevalence study in 68 ICUs across 10 European countries

• Blood samples
  • Peak, mid-dose, and trough to measure antibiotic exposure

• Data for fluconazole, caspofungin, anidulafungin
  • Considerable inter-individual variability in PK
  • One-third of fluconazole treated patients did not achieve minimum recommended PK/PD dosing target
  • Echinocandin dose optimization needed to reduce variability

Can we do better with echinocandin dosing?

Distributions of free drug AUCs for caspofungin
(14 daily doses)

Currently licensed echinocandin dosing regimens may result in suboptimal PK/PD exposures early in the course of therapy and during the treatment of less susceptible pathogens.

Median exposures and 5% and 95% percentile for FDA-approved dosing

Target AUC/MIC
C. glabrata MIC₉₀

Days of Therapy

Acquired resistance and the gastrointestinal tract
Another sign of inadequate dosing?

*Esophagus and oral mucosa*

Buccal swabs post antifungal treatment (n=93 pts)\(^1\)
21.6% anidulafungin-resistant *C. glabrata*

*Intraabdominal candidiasis; Biliary tract*

Intraabdominal candidiasis\(^2\)
FKS mutant *Candida* isolates were recovered from 24% (6/25) of abdominal candidiasis patients exposed to echinocandin

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“A person who takes medicine must recover twice, once from the disease and once from the medicine”

Sir William Osler, M.D.
1849 – 1919
Common antifungal toxicities

**Hepatic toxicity**
- All azoles
- Amphotericin B
- Cyclodextrins?
- 5FC
- Echinocandins

**Renal toxicity**
- Amphotericin B
- Voriconazole

**CNS**
- Voriconazole

**Photopsia**
- Voriconazole

**Peripheral neuropathy**
- Itraconazole, posaconazole, Voriconazole, isavuconazole?

**Periostitis**
- Voriconazole

**GI intolerance**
- Voriconazole (SCC)
- all azoles
- Posaconazole
- 5FC

**Cardiac**
- Itraconazole
- (all azoles-drug interactions)

**Infusion reactions**
- Amphotericin B
- Echinocandins

**Bone marrow/Anemia**
- 5FC
- Amphotericin B (EPO suppression)

**Adrenal effects**
- All triazoles, esp. Itraconazole, posaconazole

Posaconazole-associated hypertension and hypokalemia (iatrogenic Cushing syndrome)

- **Mechanism:** Posaconazole-inhibits 11 β-hydroxylase enzyme → resulting in elevated levels of the mineralocorticoid receptor activator deoxycorticosterone →
- Possible relationship with elevated posaconazole levels
- In clinical studies, hypokalemia 30% and incident hypertension 18%
- All patients on posaconazole therapy should be routinely screened for hypertension and hypokalemia

Trimethoprim-sulfamethoxazole toxicities

N eurological effects
(aseptic meningitis, tremor, delirium, gait disturbances)

O oxygen capacity decreased
(methemoglobinemia, blood dyscrasia, bone marrow suppression, thrombocytopenia)

T toxic epidermal necrolysis or cutaneous reactions
(drug hypersensitivity, fever, rash, exanthema)

R reproductive toxicity
(neural tube defects, cardiovascular and oral cleft, urinary tract defects)

I interactions with other drugs
(inhibition of CPY2C8, 2C9, renal OATP, OCTP)

S sugar
(hypoglycemia especially with oral hypoglycemics)

K Hyperkalemia and other kidney effects
(hyperkalemia, interstitial nephritis, obstructive tubulopathy, hyponatremia)

Y? Why not consider an alternative antimicrobial?

Up to 55% of patients must discontinue prophylaxis

Ho JM-W, Juurlink DN. CMAJ 2011; 183:1851–1858.
What are we missing?

- Novel mechanism of action
- Emerging resistance
- Adequate PK
- Toxicities
- Drug interactions
How big of problem are drug interactions? 
(>10,000 real or theoretical interactions with triazoles)

50% of medications used in oncology or transplant populations are metabolized by 3A4; many have narrow therapeutic index.

Magnitude of interaction caused by perpetrator drug

Prognostic relevance of integrated genomic profiling in acute myelogenous leukemia

an explosion of new drugs under investigation

58% of new therapies in Phase I-III clinical trials at our institute have relative or absolute contraindications use with triazoles (CYP 3A4, QTc prolongation)

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<th>Gene</th>
<th>Overall Frequency, %</th>
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<td>NPM1</td>
<td>29</td>
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<tr>
<td>DNMT3A</td>
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<td>NRAS</td>
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What are we missing?

- Novel mechanism of action
- Emerging resistance
- Adequate PK
- Toxicities
- Drug interactions
- Dosing flexibility
# Antifungal checklist

## approved therapies

<table>
<thead>
<tr>
<th>Drug</th>
<th>Novel mechanism of action</th>
<th>Activity in emerging resistance</th>
<th>Optimized PK/PD</th>
<th>Dosing flexibility</th>
<th>Limited or no toxicity</th>
<th>Few serious drug interactions</th>
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# Antifungal checklist
## looking to the future

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<th>Dosing flexibility</th>
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Summary

• We still have important gaps in the spectrum, PK/PD and safety of systemic antifungal therapy

• Emerging resistance is raising concerns about the future viability of current antifungals

• A number of investigational agents currently under development show some promise, especially for MDR pathogens