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Is it time to rethink echinocandin dosing?

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Disclosures

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• Advisory committees: Gilead, Cidara, F2G
“Medicine is a science of uncertainty, and an art of probability”

Sir William Osler, M.D.
(1849-1919)
The uncertain science of antibiotic dosing

Dosing

- Site of infection
- Patient factors
- Drug characteristics
- Intrinsic activity
- Acquired resistance

Pharmacokinetics (PK)

- Exposure variability
- Toxicity

Pharmacodynamics (PD)

- MIC variability

PK/PD Index

- Microbiologic effect

Clinical outcome

Adapted from: Theuretzbacher U. Clin Infect Dis 2012;54:1785-1792
Echinocandin exposures are variable in critically-ill patients

- Pharmacokinetic point prevalence study (n=68 ICUs):¹
  - Included patients receiving caspofungin/ anidulafungin
    - Cmax, AUC_{0-24}, Cmin ~50% lower values than reported in healthy volunteers
    - Cmax, AUC_{0-24}, Cmin ~40% lower values than reported in previous ICU PK studies

- Empirical micafungin in ICU patients with sepsis, organ failure and Candida colonization (EMPIRICUS trial):²,³
  - Empirical micafungin 100 mg/day was not associated with improved fungal-free survival vs. placebo by day 28
  - Measured micafungin blood concentrations were lower than expected → increased clearance (low albumin) and obesity⁴

Micafungin 100 mg/day probability of target attainment (PTA)*
A PK/PD autopsy of the EMPIRICUS trial

PTA* was ≥ 90% in *Candida albicans* and *Candida glabrata* infections, except when the MIC was ≥ 0.015 mg/L

Median patient weight: 84.5 kg (48-141)

*C. albicans* MIC=0.016 mg/L;
SOFA < 10

*C. albicans* MIC=0.016 mg/L;
SOFA ≥ 10 (25% decrease in clearance)


* Total micafungin AUC/MIC > 5000
Echinocandin drug penetration at the site of infection
Intraabdominal abscess model

IP infection model: $1 \times 10^7$ *C. albicans* with sterile stool

Matrix-assisted desorption ionization mass spectrometry imaging technology


Liver lesions after single dose experiment
Echinocandin drug penetration at the site of infection

Intraabdominal abscess model multiple micafungin doses

Liver lesions after 2-3 micafungin doses

Drug distribution in liver after single dose CD101 at 20 mg/kg determined by MALDI MS Imaging

Fungi location stained by GMS

Zhao, Perlin et al, AAC July 2017
Time to rethink dosing?

Yes  
Site of infection  
Patient factors

Dosing

Yes

Pharmacokinetics (PK)

Exposure variability

Toxicity

PK/PD Index

Microbiologic effect

Clinical outcome

Pharmacodynamics (PD)

MIC variability

Intrinsic activity

Acquired resistance

Drug characteristics

Adapted from: Theuretzbacher U. Clin Infect Dis 2012;54:1785-1792
Where do we find echinocandin resistance?

- Bloodstream
- GI tract
Where do we look for echinocandin resistance?

**Esophagus:**
Lower drug concentrations, high inoculum, biofilms

**Bloodstream:**
High drug concentrations, low inoculum

**Gut:**
Low drug concentrations, high inoculum, biofilms?

Where do we look for echinocandin resistance?

Oral swab surveillance after ≥ 7 days of echinocandins\(^2\)

Acquired resistance in \textit{C. glabrata} 21.6%  

\textbf{SENTRY 2006-2016, single center studies}\(^1,2\)

\textbf{Echinocandin resistance rate: 3-12\%}  

FKS mutant \textit{Candida} isolates detected in 24\% (6/25) patients exposed to echinocandins\(^4,5\)

\begin{itemize}
  \item \textit{C. glabrata} 29\%
  \item \textit{C. albicans} 14\%
\end{itemize}

\(^1\)Pfaller M et al. \textit{Open Forum Infect Dis} 2019;6 (Supplement_1):S79–94.  
The GI tract as the major source of echinocandin resistance

1.5x10^8 CFU *C. glabrata* → PIP/Tazo → Dexamethasome immunosuppression

Caspofungin 5 mg/kg (humanized dose)

↔ CFU in stool vs. control (FKS mutants in 10% mice)

No positive BC during caspofungin treatment

Organ dissemination in 60% of mice (No FKS mutants)
Mean small intestine-3.8 μg/mL
Mean large intestine-9.1 μg/mL

Caspofungin 20 mg/kg (4x humanized dose)

Transient ↓ then ↑ (100% mice with FKS mutants)

No positive BC during caspofungin treatment

Organ dissemination in 30% of mice (ALL FKS mutants)
Mean small intestine-36.2 μg/mL
Mean large intestine-22.2 μg/mL

Controls 50%

10^7-10^8 CFU/stool

Controls 70%

Time to rethink dosing?

Is our dosing optimized to address these problems?

Adapted from: Theuretzbacher U. Clin Infect Dis 2012;54:1785-1792
Currently-recommended echinocandin dosing schemes were not developed from PK/PD principles

“An additional challenge was that there was no definitive information about the PK/PD relationship for pneumocandins, making dose selection less certain.”

What have we learned about echinocandin PK/PD from animal models?

Rabbit model of invasive candidiasis

Micafungin Cmax/MIC and AUC/MIC correlate with efficacy

Micafungin dosing

Plasma micafungin mg/L

Mean AUC \(0-312\) similar for all three regimens

Larger infrequent doses maximize echinocandin antifungal activity

Neutropenic rabbit model of invasive candidiasis

*C. albicans* MIC 0.125 mg/L (CLSI)

When AUC/MIC is equivalent, dosing regimens that achieve a higher Cmax/MIC exhibit improved killing

* P< 0.05 vs. control

Echinocandins are not fungicidal against *C. glabrata* in neutropenic models at currently recommended doses.

**Humanized dosing, neutropenic murine model of *C. glabrata* fungemia (MIC 0.06 mg/L)**

Clinical pharmacodynamic index identification for micafungin in esophageal candidiasis: Dosing strategy optimization

<table>
<thead>
<tr>
<th>Micafungin dosing regimen</th>
<th>Mycological response at EOT?*</th>
<th>Clinical relapse at 2 weeks?**</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Success (n=260)</td>
<td>Yes (n=29)</td>
</tr>
<tr>
<td>150 mg QD</td>
<td>145 (78.8)</td>
<td>22 (12.2)</td>
</tr>
<tr>
<td></td>
<td>39 (21.2)</td>
<td>159 (87.9)</td>
</tr>
<tr>
<td>300 mg QOD</td>
<td>115 (87.1)</td>
<td>7 (5.6)</td>
</tr>
<tr>
<td></td>
<td>17 (12.9)</td>
<td>119 (94.4)</td>
</tr>
<tr>
<td>Total</td>
<td>184</td>
<td>181</td>
</tr>
<tr>
<td></td>
<td>22 (12.2)</td>
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<td>Total</td>
<td>181</td>
<td>181</td>
</tr>
</tbody>
</table>

\[P=0.056\] \[P=0.051\]

The dosing regimen that achieves a higher Cmax/MIC was associated with improved clinical success and lower relapse rates.

Caspofungin 70/50 vs. 150 mg/day for adult patients with invasive candidiasis

Conclusion: Both dosing regimens were equivalent and safe

Design hypothesis: Higher caspofungin dose is safe and non-inferior Δ <15%.
Study was not powered to evaluate superiority of caspofungin higher dose
Multicenter double-blind trial of caspofungin 70/50 vs. 150 mg/day for adult patients with invasive candidiasis

Favors 70/50  Favors 150

Comparison of caspofungin vs. rezafungin
PK/PD target attainment (C. glabrata MIC 0.25 mg/L)

Caspofungin (14 daily doses)

<table>
<thead>
<tr>
<th>Days of Therapy</th>
<th>Free-drug Plasma AUC0-24: MIC Ratio</th>
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<tbody>
<tr>
<td>1</td>
<td>70mg</td>
</tr>
<tr>
<td>7</td>
<td>50mg</td>
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</table>

Rezafungin (4 weekly doses)

<table>
<thead>
<tr>
<th>Weeks of Therapy</th>
<th>Weekly fAUC:MIC Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>400mg</td>
</tr>
<tr>
<td>2</td>
<td>200mg</td>
</tr>
<tr>
<td>3</td>
<td>200mg</td>
</tr>
<tr>
<td>4</td>
<td>200mg</td>
</tr>
</tbody>
</table>

Target fAUC/MIC

MIC=0.25 for caspofungin. MIC=0.12 for CD101
Bader et al. Overcoming the Resistance Hurdle: PK-PD Target Attainment Analyses of Rezafungin (CD101) for Candida albicans and Candida glabrata. Submitted AAC 2018; revised with Phase 2 results.
Novel echinocandin dosing approaches during micafungin prophylaxis

- Intermittent administration of higher-dose micafungin (≥ 5 doses of 300 mg 2-3 times weekly) was well tolerated in patients with acute leukemia and allogeneic SCT recipients\(^1\)

- Intermittent higher-dose micafungin was safe in children\(^2,3\)

- Equivalent weekly AUCs have been confirmed for 300 mg twice weekly dosing of micafungin (3hr infusion) → possible 700 mg once weekly? \(^4\)

Summary

• Preclinical and clinical evidence suggest current echinocandin dosing approaches need revision for some patient groups

• Acquired echinocandin resistance can be detected at much higher frequency in the GI tract than bloodstream, and likely serves as a reservoir for future breakthrough infection

• Evidence that PK/PD optimization of echinocandin dosing might improve clinical efficacy, reduce relapse, and enhance dosing convenience
Thank you!

“The Great Wave of Candida”
Cristina Marcos

The Great Wave off Kanagawa
Katsushika Hokusai