general, and not from any systematic problem with the gradient methods. In the other instance, a BLPAR strain was designated ampicillin-susceptible by Etest (MIC = 1 mg/L), ampicillin- intermediate by M.I.C.E. (MIC = 2 mg/L) and ampicillin-resistant by BMD (MIC = 16 mg/L). As stated earlier, the low MICs when gradient methods were used were because of a faint growth within the inhibition zone that was difficult to detect at 24 h.

In contrast to the findings of Billal et al., all of the β-lactam MIC results for BLNAR and BLPACR strains in this study using either Etest or M.I.C.E. were within +2 doubling dilutions of the BMD method, and the gradient methods produced results comparable to each other and to the BMD method. Despite this, given the findings of both Billal et al. and Kim et al., it would be prudent for any unexpectedly high β-lactam MICs determined by the gradient methods to be repeated by the reference CLSI BMD method.

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**Transparency declarations**

None to declare.

**References**


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**Comparison of killing activity of caspofungin against Candida parapsilosis, Candida orthopsilosis and Candida metapsilosis**

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Candida parapsilosis

Comparison of killing activity of caspofungin against *Candida parapsilosis*.
In the killing studies using RPMI-1640, caspofungin showed a fungistatic effect in the case of \textit{C. parapsilosis} and \textit{C. orthopsilosis} after 24 h (Table 1). However, CP85 \textit{C. orthopsilosis} was killed by 2 mg/L (16×MIC) caspofungin, but not by any other concentrations. After 48 h, decreases in viable cfu numbers at 1–16 mg/L caspofungin concentrations for \textit{C. parapsilosis} and \textit{C. orthopsilosis} varied between 1.07 and 2.95 log\textsubscript{10} cfu/mL and between 1.18 and 2.97 log\textsubscript{10} cfu/mL, respectively. After 48 h, caspofungin was fungicidal at concentrations of 1–8 mg/L (16–128×MIC) against all \textit{C. metapsilosis} isolates apart from isolate number CP92.

In killing studies with AM3, a fungistatic effect was observed after 24 h; two of the seven \textit{C. parapsilosis} isolates showed PG (Table 1). After 48 h, four of the seven \textit{C. parapsilosis} isolates were killed at ≥0.5 mg/L caspofungin concentrations (≥0.5–2×MIC); the remaining three isolates (isolates 9150, 896/1 and CP117) showed PG. All \textit{C. orthopsilosis} isolates showed PG after 24 h (Table 1). However, after 48 h, all isolates were killed by caspofungin concentrations of 0.12–1 mg/L (2–16×MIC) or higher. All \textit{C. metapsilosis} strains were killed at caspofungin concentrations of ≥1 mg/L after 48 h, but not after 24 h (Table 1).

In our work, the three \textit{C. orthopsilosis} isolates behaved similar to \textit{C. parapsilosis} after 24 h; fungistatic or PG effects were observed regardless of the medium used. However, in AM3 after 48 h, caspofungin proved to be clearly fungicidal against \textit{C. orthopsilosis}, but not against \textit{C. parapsilosis} isolates.

### Table 1. Influence of solvent on killing activity of caspofungin (CAS) against \textit{C. parapsilosis}, \textit{C. orthopsilosis} and \textit{C. metapsilosis} isolates

<table>
<thead>
<tr>
<th>Isolate number</th>
<th>RPMI-1640 MIC\textsuperscript{a} (mg/L)</th>
<th>CAS effect in time–kill studies</th>
<th>MIC\textsuperscript{a} (mg/L)</th>
<th>Antibiotic medium 3 CAS effect in time–kill studies</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>after 24 h</td>
<td>after 48 h</td>
<td>after 24 h</td>
<td>after 48 h</td>
</tr>
<tr>
<td>\textit{C. parapsilosis}</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ATCC 22019</td>
<td>0.5fungistatic</td>
<td>fungistatic</td>
<td>0.25fungistatic</td>
<td>fungistatic</td>
</tr>
<tr>
<td>9150 (Hungary, blood)</td>
<td>1–2fungistatic</td>
<td>fungistatic</td>
<td>0.25fungistatic</td>
<td>fungicidal at ≥0.5 mg/L PG\textsuperscript{b} started at 8 mg/L fungicidal at ≥0.12 mg/L fungicidal at ≥0.25 mg/L</td>
</tr>
<tr>
<td>509 (Hungary, throat)</td>
<td>0.5fungistatic</td>
<td>fungicidal at 16 mg/L</td>
<td>0.25–0.5PG\textsuperscript{b} started at 1 mg/L fungicidal at ≥0.12 mg/L fungicidal at ≥0.25 mg/L</td>
<td></td>
</tr>
<tr>
<td>2845 (Hungary, blood)</td>
<td>0.5–1fungistatic</td>
<td>fungistatic</td>
<td>0.25PG\textsuperscript{b} started at 16 mg/L fungicidal at ≥0.25 mg/L</td>
<td></td>
</tr>
<tr>
<td>896/1 (Hungary, wound)</td>
<td>1–2fungistatic</td>
<td>fungicidal at 16 mg/L</td>
<td>0.25–0.5fungistatic</td>
<td>fungicidal at ≥1 mg/L PG\textsuperscript{b} started at 16 mg/L</td>
</tr>
<tr>
<td>CP120 (Italy, faeces)</td>
<td>0.5fungistatic</td>
<td>fungicidal at 16 mg/L</td>
<td>0.25fungistatic</td>
<td>fungicidal at ≥1 mg/L PG\textsuperscript{b} started at 16 mg/L</td>
</tr>
<tr>
<td>CP117 (Italy, nail)</td>
<td>0.5–1fungistatic</td>
<td>fungistatic</td>
<td>0.25fungistatic</td>
<td>fungicidal at ≥1 mg/L</td>
</tr>
<tr>
<td>\textit{C. orthopsilosis}</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CP85 (Italy, catheter)</td>
<td>0.12fungistatic\textsuperscript{c}</td>
<td>fungistatic\textsuperscript{c}</td>
<td>0.06PG\textsuperscript{b} started at 16 mg/L fungicidal at ≥0.12 mg/L fungicidal at ≥0.12 mg/L</td>
<td></td>
</tr>
<tr>
<td>CP25 (Italy, nail)</td>
<td>0.12–0.25fungistatic</td>
<td>fungicidal at 16 mg/L</td>
<td>0.06PG\textsuperscript{b} started at 8 mg/L fungicidal at ≥0.12 mg/L</td>
<td></td>
</tr>
<tr>
<td>CP125 (Italy, nail)</td>
<td>0.12fungistatic</td>
<td>fungicidal at 16 mg/L</td>
<td>0.06PG\textsuperscript{b} started at 8 mg/L fungicidal at ≥0.12 mg/L</td>
<td></td>
</tr>
<tr>
<td>\textit{C. metapsilosis}</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CP5 (Italy, sputum)</td>
<td>0.25fungicidal at ≥4 mg/L</td>
<td>fungicidal at ≥1 mg/L</td>
<td>0.06fungicidal at ≥0.06 mg/L fungicidal at ≥0.06 mg/L</td>
<td></td>
</tr>
<tr>
<td>CP92 (Italy, faeces)</td>
<td>0.5fungistatic</td>
<td>fungicidal at ≥1 mg/L</td>
<td>0.03–0.06PG\textsuperscript{b} started at 16 mg/L fungicidal at ≥0.06 mg/L</td>
<td></td>
</tr>
<tr>
<td>CP86 (Italy, vagina)</td>
<td>0.25fungicidal at ≥8 mg/L</td>
<td>fungicidal at ≥8 mg/L</td>
<td>0.03–0.06fungicidal at ≥0.5 mg/L fungicidal at ≥0.06 mg/L</td>
<td></td>
</tr>
<tr>
<td>12821 (Hungary, blood)</td>
<td>0.12–0.25fungicidal at ≥4 mg/L</td>
<td>fungicidal at ≥1 mg/L</td>
<td>0.03–0.06fungicidal at ≥0.5 mg/L fungicidal at ≥0.06 mg/L</td>
<td></td>
</tr>
</tbody>
</table>

\textsuperscript{a}Ranges show the results of two independent experiments.

\textsuperscript{b}Paradoxical growth.

\textsuperscript{c}This isolate was killed at a caspofungin concentration of 2 mg/L.
C. metapsilosis isolates, regardless of the medium used, were more susceptible to the killing activity of caspofungin.

This study is the first comparing caspofungin killing activity against the closely related species C. parapsilosis, C. orthopsilosis and C. metapsilosis. Killing curves, regardless of the medium used, showed a decreasing order of susceptibility to caspofungin: C. metapsilosis > C. orthopsilosis > C. parapsilosis.

Based on high echinocandin MICs for C. parapsilosis sensu stricto, in the case of isolates identified as C. parapsilosis sensu lato low MICs of echinocandins may be regarded as an indicator that an isolate is in fact C. orthopsilosis or C. metapsilosis; in the case of isolates with low echinocandin MICs, DNA-based identification1–3 of the isolates is desirable. Because C. orthopsilosis and C. metapsilosis seem to be relevant species among bloodstream isolates in some countries,2,3 this distinction may be particularly important in some epidemiological situations or in clinical situations when the use of echinocandins as therapy or prophylaxis is planned.

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Posaconazole concentrations in the central nervous system

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Keywords: invasive fungal infections, antifungal therapy, FungiScope, plasma drug levels, therapeutic drug monitoring

Sir,

Posaconazole is a new triazole approved for prophylaxis in neutropenic high-risk patients1,2 and as salvage treatment of, for example, invasive aspergillosis.3 Pharmacokinetic analyses suggest an exposure–response relationship,3 diarrhoea, proton pump inhibitors (PPIs) and elevated gamma-glutamyl-transferase are associated with reduced plasma concentrations.5

We report the first three patients in whom posaconazole concentrations in the CNS were determined and related to their respective serum concentrations.

Patient A

A 46-year-old male taking prophylactic posaconazole 200 mg three times a day and prednisone 75 mg intravenously (iv) twice daily for extensive graft-versus-host disease with severe diarrhoea presented with tenderness over the right maxillary sinus accompanied by paresis of cranial nerves III, IV and VI, acute loss of visual acuity of the left eye and a C-reactive protein (CRP) increase to 253 mg/dL. Cranial MRI revealed a space-occupying lesion in the right maxillary sinus and an occluded right internal carotid. The same day, the patient underwent surgery of the maxillary sinuses. Histopathological examination