Central Venous Catheters and Candidemia: Remove them All!

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What this discussion is and isn’t about:

• Removal of central venous catheters, including percutaneous, tunneled, and other surgically placed venous access devices
• It is not about peripheral catheters
• It is not about arterial catheters
• It is not about vascular shunts for hemodialysis
• It is not about other intravascular devices
The Status Quo:

- In clinical trials, the vast majority (approx 70-80%) of cases of candidemia occur among patients with indwelling central venous catheters.
- While not always the cause of candidemia, retention of these catheters is associated with a greater length of candidemia in several large randomized trials.
- Higher mortality is reported among patients with retained catheters in selected comparative trials.
- Anecdotal reports recognize patients in whom candidemia was not cleared until the CVC was removed.
- Despite these less than perfect data, all clinical trials since Rex 1994 have mandated early CVC removal as part of patient management.
Problems Associated with CVC Removal

- There are a few....bleeding, requirement for anesthesia (local or general) for imbedded catheters, local pain
- No other major risks associated with CVC removal
Problems Associated with CVC Replacement

- It is usually time-consuming
- Limited alternative access sites
- Risk of bleeding (esp among pts with thrombocytopenia)
- Risk of infection
- Other risks associated with procedure
- Not everyone is a suitable candidate
What Are Biofilms?

- Structured microbial communities characterized by irreversible attachment to an artificial surface; organisms become embedded in a matrix of extracellular polymeric substances produced by these cells.

- Organisms demonstrate phenotypic traits distinct from planktonic strains, notably resistance to antimicrobial therapy.
Andes et al, Infect Immun 2004
The Role of Biofilms in Candidemia

- Biofilms probably play a pivotal role in the persistence of candidemia among pts with retained CVCs
- Among *Candida* spp, resistance genes are upregulated in the biofilm matrix (eg fluconazole efflux pumps, CDR1 and CDR2)
- Most biofilm-associated *Candida* spp retain susceptibility to echinocandins and lipid formulations of AmB
1,3 β-D Glucan Levels

Nett J et al JID 2007 195:1705-12
Now, let’s look at some data from several clinical trials evaluating therapy for candidemia......
Candidemia I\textsuperscript{1,2}

- 206 evaluable nonneutropenic pts with candidemia (78\% of pts with CVCs)
- Investigators strongly encouraged to remove CVCs as early as possible
- Removal/replacement over a wire was discouraged
- Duration of candidemia was 2.6d vs 5.6d (p<.001) for complete exchange vs none
- Pts without exchange has higher APACHE II scores, more catheters
- Individual cases of failure to clear bloodstream asso with retained catheters of all types (central, peripheral, arterial)

\textsuperscript{1}Rex et al, NEJM 1994;331:1325
\textsuperscript{2}Rex et at CID 1995;21:994
High vs Low-dose AmB, AmB vs Flu

- Not a formal randomized, double blind study- more of an observational study
- Two studies in one: high vs low dose AmB; and AmB vs Flu
- 427 consecutive pts enrolled
- Mortality was 21% vs 41% (p<.001) among pts with catheter removal vs none

Candidemia in Neonates

- 50 neonates with candidemia given AmB, randomized to early CVC removal (within 3d) vs late CVC removal (>3d)
- Mortality difference in ER vs LR for neonates with \textit{C. albicans} fungemia: 0/21 (0%; CI 0-14%) vs 9/23 (39%, CI 19-59%)

Karlowicz et al Pediatrics 2000;106;e63
Candidemia II

- Similar criteria for enrollment, outcome as Candidemia I
- 219 pts met ITT criteria
- >90% with recent CVCs
- Complete catheter exchange resulted in clearance of bloodstream 1 day sooner compared to pts with no complete exchange (p=.08)
- No difference in APACHE II scores

Rex et al, CID 2003;36:1221
Anidulafungin vs. Fluconazole

- Randomized, double blind study of pts with candidemia (97% non-neutropenic)
- 78% with CVC at baseline
- Most CVCs removed at or near study entry (93%)
- 3 of 4 (75%) anidulafungin vs 3 of 11 (27%) fluconazole recipients without catheter removal were successfully treated
- No firm conclusions, but suggestive of poor effect of fluconazole on catheter associated candidemia

Reboli et al NEJM 2007;356:2472
Micafungin vs Caspofungin

- Largest candidemia study to date
- Three arm, randomized, double-blind trial comparing mica 100, mica 150, and caspo 50 for invasive candidiasis
- 595 evaluable pts, 40 were neutropenic
- CVC removal strongly advised at study entry and within 3 days of randomization
- Similar eligibility criteria, outcome measures as previous studies

Pappas PG et al CID 2007:45;883
### Table 5. Characteristics of patients for whom treatment was successful.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Micafungin arms</th>
<th></th>
<th>Caspofungin arm</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>100 mg arm (n = 191)</td>
<td>150 mg arm (n = 199)</td>
<td>Caspofungin arm (n = 189)</td>
<td></td>
</tr>
<tr>
<td>Candidemic</td>
<td>124/163 (76.1)</td>
<td>125/168 (74.4)</td>
<td>118/161 (73.3)</td>
<td>.85</td>
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<tr>
<td>Noncandidemica</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>22/28 (78.6)</td>
<td>16/33 (53.3)</td>
<td>17/26 (65.4)</td>
<td>.14</td>
</tr>
<tr>
<td>Acute disseminated</td>
<td>6/7 (85.7)</td>
<td>3/11 (27.3)</td>
<td>5/8 (62.5)</td>
<td>.06</td>
</tr>
<tr>
<td>Peritonitis</td>
<td>4/6 (66.7)</td>
<td>4/7 (57.1)</td>
<td>2/5 (40.0)</td>
<td></td>
</tr>
<tr>
<td>Abscess</td>
<td>5/5 (100.0)</td>
<td>5/5 (83.3)</td>
<td>5/9 (66.7)</td>
<td>.42</td>
</tr>
<tr>
<td>Choroiditis</td>
<td>4/6 (66.7)</td>
<td>2/4 (50.0)</td>
<td>1/1 (100.0)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>3/4 (75.0)</td>
<td>2/2 (100.0)</td>
<td>3/3 (100.0)</td>
<td></td>
</tr>
<tr>
<td>Candida species recovered at baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C. albicans</td>
<td>71/102 (77.2)</td>
<td>71/102 (60.6)</td>
<td>61/83 (73.5)</td>
<td>.5</td>
</tr>
<tr>
<td>Non-C. albicans</td>
<td>78/104 (75.0)</td>
<td>73/102 (71.6)</td>
<td>81/114 (71.1)</td>
<td>.78</td>
</tr>
<tr>
<td>C. glabrata</td>
<td>24/29 (85.7)</td>
<td>30/34 (88.2)</td>
<td>22/33 (66.7)</td>
<td>.07</td>
</tr>
<tr>
<td>C. tropicalis</td>
<td>21/31 (67.7)</td>
<td>20/33 (60.6)</td>
<td>24/32 (75.0)</td>
<td>.5</td>
</tr>
<tr>
<td>C. parapsilosis</td>
<td>22/29 (75.9)</td>
<td>15/21 (71.4)</td>
<td>27/42 (64.3)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>C. kruisci</td>
<td>0/0 (0.0)</td>
<td>5/8 (62.5)</td>
<td>3/4 (75.0)</td>
<td>.59</td>
</tr>
<tr>
<td>Other</td>
<td>10/14 (71.4)</td>
<td>6/12 (50.0)</td>
<td>10/12 (83.3)</td>
<td></td>
</tr>
<tr>
<td>WBC count at baseline, cells/mm³</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>&lt;500</td>
<td>18/22 (81.8)</td>
<td>9/17 (52.9)</td>
<td>7/11 (63.6)</td>
<td>.14</td>
</tr>
<tr>
<td>≥500</td>
<td>128/169 (75.7)</td>
<td>133/182 (73.1)</td>
<td>129/177 (72.9)</td>
<td>.8</td>
</tr>
<tr>
<td>APACHE II score at baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤20</td>
<td>125/156 (80.1)</td>
<td>129/153 (75.5)</td>
<td>115/152 (75.7)</td>
<td>.54</td>
</tr>
<tr>
<td>&gt;20</td>
<td>21/35 (60.0)</td>
<td>22/43 (55.0)</td>
<td>21/36 (58.3)</td>
<td>.91</td>
</tr>
<tr>
<td>Intravascular catheter present at baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Removed, time after baseline</td>
<td>100/120 (83.3)</td>
<td>102/133 (73.4)</td>
<td>97/125 (77.6)</td>
<td>.16</td>
</tr>
<tr>
<td>≤24 h</td>
<td>36/46 (78.3)</td>
<td>37/51 (72.5)</td>
<td>38/49 (77.6)</td>
<td></td>
</tr>
<tr>
<td>25–48 h</td>
<td>19/23 (82.6)</td>
<td>15/21 (71.4)</td>
<td>14/18 (77.8)</td>
<td></td>
</tr>
<tr>
<td>&gt;48 h</td>
<td>45/51 (89.2)</td>
<td>50/67 (74.6)</td>
<td>45/50 (77.6)</td>
<td></td>
</tr>
<tr>
<td>Not removed</td>
<td>29/47 (61.7)</td>
<td>32/47 (68.1)</td>
<td>30/50 (60.0)</td>
<td>.75</td>
</tr>
</tbody>
</table>
Current Recommendations Regarding CVC Management in Candidemia

- For non-neutropenic patients: ‘…intravenous catheter removal is strongly recommend in nonneutropenic pts with candidemia.’ (AII)
- For neutropenic patients: ‘…intravenous catheter removal should be considered.’ (BIII)

So, what’s the answer?

• It is dangerous to be too dogmatic about this issue....every pt should be managed individually.
• For most non-neutropenic pts with candidemia and a CVC, the catheter can and should be removed.
• Neutropenic pts are more challenging....the CVC should be removed if it can be done without significant risk, and another source of candidemia has been reasonably excluded.
• For pts with implanted catheters and tunnel infection due to *Candida*, removal is always necessary.
• For pts with candidemia due to *C. parapsilosis*, CVC removal is almost always necessary, independent of neutrophil count.
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