Background

- Candidemia is generally accepted as the most common type of invasive candidiasis (IC), and it accounts for the overwhelming majority of cases included in clinical trials and other studies. Other types of IC are less well-characterized.
- A review at our center in 2010-2011 demonstrated that deep-seated candidiasis (DSC) accounted for 65% of IC, compared to only 35% for candidemia. Moreover, intra-abdominal candidiasis (IAC) represented 83% and 60% of DSC and IC, respectively.
- Our data and the limited published experience suggest that IAC is more common than recognized, and is associated with significant morbidity and mortality.
- The diagnosis of both IAC and candidemia is limited by the poor sensitivity of blood culture, the diagnostic gold standard.
- Intra-abdominal cultures are also limited by poor sensitivity, and they are often delayed or contraindicated by patients' conditions.
- The development of a rapid, blood-based diagnostic test that is sensitive for blood culture-negative candidiasis is a top priority.
- T2Candida assay is a non-culture, whole blood Candida detection system with limit of detection = 1 CFU/mL (Neely, Sci Transl Med 2014; 5:182ra54).

Objectives

- To present a case that highlights important clinical features of IAC, and the difficulty in making timely diagnosis.
- To describe the epidemiology, risk factors, treatment and outcome of patients with IAC.

Methods

- Observational study of patients at our center with ≥1 sterile site culture positive for Candida spp. over 15 months (2011-12).
- Case report of a patient enrolled in a diagnostic trial of T2Candida assay.

- T2Candida assay and T2Dx instrument makes diagnoses of candidiasis within ~3 hrs, testing whole blood directly in a one-step automated process (Beyda, Diagn Microbiol Infect Dis 2013; 77:324).

Definitions

- Intra-abdominal candidiasis (IAC): steriley-collected abdominal fluid cultures that are positive for Candida spp., in the setting of signs and symptoms consistent with an active infection.
- Intra-abdominal infection (IAI) refers to intra-abdominal abscesses (IAA) and peritonitis, which can be due to bacteria or Candida. Peritonitis is defined as infected fluid in the peritoneal cavity with evidence of an inflammatory response. IAA is defined as a localized pocket of infection that is walled-off by the host inflammatory response.
- IAC was classified as: Primary (spontaneous or dialysis-associated), Secondary (seeded from GI tract during perforation or surgery), Tertiary (persistence/recurrence after seemingly adequate treatment).

Case report

- A liver transplant recipient with negative blood cultures for Candida and bacteria was enrolled as a control in a multi-center diagnostic trial of the T2Candida assay.
- He was treated with voriconazole targeted prophylaxis, per UPMC protocol (Eschenauer, Am J Transplant 2014; in press).

- He developed a perihepatic abscess, but was too unstable for drainage. He was treated with broad-spectrum antibiotics and voriconazole + caspofungin; 12 blood cultures were negative.
- T2Candida assay on whole blood was positive for C. albicans. The diagnosis was confirmed 7 days later by culture of surgical drainage.
- He completed a course of caspofungin.
- T2Candida shortened the time to diagnosis of blood culture-negative IAC.

Results

- Small bowel, 27%
- Colon, 27%
- Pancreas, 18%
- Liver, 9%
- Gastric, 8%
- Gall bladder, 3%

Microbiology

- All pts had (+) IA cultures for Candida
- Only 4% had (+) blood cultures
- 65% of IAC were co-infected with bacteria (see above)

Treatment and Outcomes

- All patients were treated with percutaneous (59%) or surgical (41%) drainage.
- 73% received an antifungal agent (Flucnozole, 68%; Caspofungin, 25%; Voriconazole, 5%).
- 100% received an antibacterial agent.
- Mortality rate: 23%
  - IAC from GI perforation: 50%
  - IAC from other causes: 11% (p = 0.046)
- Among survivors, 27% developed tertiary IAC, requiring multiple surgeries and prolonged antifungal agents.

Risk factors for FKS mutations among UPMC Candida isolates

Characteristics of patients infected with FKS mutants

<table>
<thead>
<tr>
<th>Isolate</th>
<th>Underlying Disease</th>
<th>Days of Prior Ec</th>
<th>FKS Mutations</th>
<th>Caspofungin MIC</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ca 874</td>
<td>DM, Obesity</td>
<td>8</td>
<td>FKS1 – R674F</td>
<td>0.12</td>
<td>Failure</td>
</tr>
<tr>
<td>Ca 1018</td>
<td>Multicore teg</td>
<td>68</td>
<td>FKS1 – S44P</td>
<td>16</td>
<td>Failure</td>
</tr>
<tr>
<td>Ca 102</td>
<td>Short gut syndrome</td>
<td>46</td>
<td>FKS2 – R650G</td>
<td>8</td>
<td>Success</td>
</tr>
<tr>
<td>Ca 35</td>
<td>Multicore teg</td>
<td>102</td>
<td>FKS2 – R650L</td>
<td>1</td>
<td>Failure</td>
</tr>
<tr>
<td>Ca 129</td>
<td>Chronic’s Disease</td>
<td>9</td>
<td>FKS2 – R650L</td>
<td>1</td>
<td>Failure</td>
</tr>
<tr>
<td>Ca 187</td>
<td>Chronic’s disease</td>
<td>171</td>
<td>FKS2 – R650L</td>
<td>2</td>
<td>Failure</td>
</tr>
<tr>
<td>Ca 209</td>
<td>Liver teg</td>
<td>64</td>
<td>FKS1 – D63RH</td>
<td>2</td>
<td>Failure</td>
</tr>
<tr>
<td>Ca 999</td>
<td>Multicore teg</td>
<td>122</td>
<td>FKS2 – G663P</td>
<td>16</td>
<td>Failure</td>
</tr>
<tr>
<td>Ca 755</td>
<td>Exophaged CA : GI Per</td>
<td>7</td>
<td>FKS2 – R650S</td>
<td>0.5</td>
<td>Not treated</td>
</tr>
</tbody>
</table>

59% (30/51) of isolates were collected from patients with prior echinocandin exposure.

20% (6/30) of isolates from patients with prior echinocandin exposure harbored FKS mutations.

5 C. glabrata (3 FKS1, 2 FKS2), 1 C. albicans

FKS mutations occurred more commonly among patients with abdominal candidiasis (20%, 6/30) than candidemia (10%, 9/89), p = 0.20.

Breakthrough candidiasis was more common 27% (14/51) versus 8% (18/251), p = 0.0006.

Conclusions

- IAC was the most common cause of IC at our center, and was associated with high mortality (especially following perforation), need for repeated surgeries, and emergence of antifungal resistance.
- All patients require antifungal therapy in addition to drainage, as clinicians cannot reliably identify patients who can be cured with drainage alone.
- Blood cultures have poor sensitivity, and IAC is under-recognized because of a dependence on intra-abdominal cultures for diagnosis.
- T2Candida assay can rapidly identify patients with IAC in whom blood cultures are negative, using whole blood and not requiring an intra-abdominal sample.
- Since collection of intra-abdominal samples is often delayed or contra-indicated, T2Candida assay can shorten time to diagnosis of IAC in addition to improving the sensitivity of diagnosis.