fungal endocarditis

Focus on Candida endocarditis

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Fungal endocarditis: evidence in the world literature (1950-2000)

**Host**
- Male to female ratio 2
- Mean age 44 +/- 14 years
- Main risk factors
  - prosthetic valve 45%
  - CVCs, 30%
  - antibiotics, 20%
  - i.v. addiction, 4%

**Pathogens**
- *Candida* spp 50-80%
- *Aspergillus* spp 20-25%
- Other
  - *Histoplasma*
  - *Coccidioides*
  - *Blastomyces*
  - *Cryptococcus*
Risk factors for *Aspergillus* endocarditis


1. Underlying cardiac abnormalities  41%
2. Prosthetic valves  39%
**Aspergillus endocarditis cases reported in the medical literature between 1950 and 2009**


<table>
<thead>
<tr>
<th>Feature</th>
<th>n. cases/total cases, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>30/53, 57%</td>
</tr>
<tr>
<td>Negative blood cultures</td>
<td>41/53, 96%</td>
</tr>
<tr>
<td>Vegetations at echo</td>
<td>26/53, 49%</td>
</tr>
<tr>
<td>- mitral valve</td>
<td>25/53, 49%</td>
</tr>
<tr>
<td>- aortic valve</td>
<td>24/53, 45%</td>
</tr>
<tr>
<td>- tricuspid valve</td>
<td>9/13, 19%</td>
</tr>
<tr>
<td>- pulmonic valve</td>
<td>1/53, 2%</td>
</tr>
<tr>
<td>- cardiac leads</td>
<td>5/53, 17%</td>
</tr>
<tr>
<td>- multivalve involvement</td>
<td>11/53, 21%</td>
</tr>
<tr>
<td>Emboli*</td>
<td>40/53, 75%</td>
</tr>
<tr>
<td>Survival</td>
<td>15/53, 29%</td>
</tr>
<tr>
<td>- medical/surgical rx</td>
<td>13/34, 38%</td>
</tr>
<tr>
<td>- medical rx alone</td>
<td>2/14, 14%</td>
</tr>
<tr>
<td>- no therapy</td>
<td>0/5, 0%</td>
</tr>
</tbody>
</table>

* Emboli involved pulmonary, ophthalmic, cerebral, iliac, coronary, hepatic, splenic, renal, brachial, and/or mesenteric arteries
**Aspergillus endocarditis spectrum of the disease**

**Device associated endocarditis** (PVE or PME)

- FUO
- Negative BC
- Emboli: 70%
- Disseminated disease: a complication of systemic emboli
- Peri-annular myocarditis (PVE)
- Mortality: near 50%

**Solid organ or bone marrow associated endocarditis**

- Fever obscured by immunosuppression
- Negative BC
- Emboli: 70%
- Disseminated disease: 75%-100%
- Diffuse myocarditis
- Mortality: near 100%
Candida endocarditis: A multifaced disease
An unusual case of catheter-related right-sided endocarditis, endophthalmitis, and extensive folliculitis, apparently caused by a single DNA biotype of *Candida albicans*, was successfully treated with a 6-month course of fluconazole.

The patient was a 21-year-old man who underwent colectomy for diffuse polyposis and developed the aforementioned syndrome following total parenteral nutrition for the treatment of purulent anorectal sinus tracts.
A 62 year old man underwent emergency aortic valve replacement for haemodynamic decompensation during E. faecalis endocarditis.

Day VI: E. cloacae VAP requiring a 9 day iv imipenem therapy course.

Day XIV: C. albicans fungemia treated with a 21 day fluco therapy course; TEE 1.5 months after antifungal therapy: OK.

8 days after fluco therapy: admission in a medical ward for massive bleeding in the right leg, low fever.. C. albicans is isolated from blood cultures.

TEE: 15 x 13 mm vegetation & aortic valve leakage.
A 76-year-old male patient, with COPD, diabetes and hypertension, came with a history of drowsiness for last 10 days. He underwent three abdominal surgeries during previous 16 months for sigmoid volvulus with intestinal obstruction due to an adenocarcinoma.

On examination, patient was pale, febrile, conscious, drowsy, dehydrated, and hypotensive.

A new systolic murmur was heard during auscultation. TTE showed large vegetation (14 × 12 mm) on the mitral valve. Moderate to severe mitral regurgitation was seen. EF 40%. Multiple blood cultures yielded *Candida* species.

Five days after admission, the patient developed AV complete block and died despite attempts of resuscitation.

Autopsy report: *C. tropicalis* endocarditis and myocarditis; septic emboli involving multiple organs.
Candida endocarditis: the extent of the problem
Endocarditis after candidemia
prospective observational one year study (2004) in 7 nord east french hospitals
Talarmin JP et al Mycoses, 2008

- Candidemia episodes: 190
- Age (median): 65 yrs
- Candida
  - albicans: 55%
  - glabrata: 19%
  - parapsilosis: 13%
- Endocarditis: 7, 3.6%
Candida endocarditis
magnitude of the problem among NVE & PVE in ICE studies
(61 centers of 28 countries)

NVE

From Jan 2000 to Aug 2005:
4 (0.25%) out of 1622 NVE cases (533 HCA NVE).
All candida IE were “non nosocomial HCA NVE”.

PVE

From Jun 2000 to Aug 2005:
23 (4.1%) out of 556 PVE cases
9.4% classified as “early PVE”, 4.3% “intermediate PVE”, and 3.3% “late PVE”
Candida endocarditis

- Etiologies and risk factors
- Pathogenesis
- Clinical outcomes
- Therapy
Candida endocarditis: systematic literature review from 1997 to 2014 and analysis of 29 cases from the SEI* Italian cohort study

* SEI: Studio Endocardite Infettiva (Infectious Endocarditis Study)
Inclusion and exclusion criteria

- Diagnosis of histologically proven IE and/or definite IE according to the modified Duke criteria [1].
- Diagnosis of CE only, with the exclusion of bacterial causes of IE or other fungal etiologies.
- Patients with definite [1] CE from the Italian Study on Endocarditis (SEI) [2] were also included.
- Cases of pacemaker- or implantable cardioverter/defibrillator (ICD)-related CE were excluded.

Definition of treatment regimens

- **Effective anti-biofilm (EAB) antifungal regimen**: administration of any drug (echinocandin or ampho B) effective against candidal biofilm at any point during treatment.
- **Combination antifungal therapy** if the patient received >1 day of two antifungal drugs concomitantly any time during therapy.
- **Chronic suppressive antifungal therapy**: terminal azole treatment for at least 6 months (Smego RA & Ahmad H *Medicine* 90: 237, 2011)
Highly active anti-biofilm (HAAB) and moderately active anti-biofilm (MAAB) antifungal therapy


<table>
<thead>
<tr>
<th></th>
<th>Anidula</th>
<th>Caspo</th>
<th>Ampho B</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>C. albicans</em></td>
<td>0.125</td>
<td>0.5</td>
<td>&gt; 32</td>
</tr>
<tr>
<td><em>C. parapsilosis</em></td>
<td>1</td>
<td>8</td>
<td>&gt; 32</td>
</tr>
<tr>
<td><em>C. tropicalis</em></td>
<td>0.06</td>
<td>1</td>
<td>32</td>
</tr>
<tr>
<td><em>C. glabrata</em></td>
<td>0.06</td>
<td>0.5</td>
<td>16</td>
</tr>
<tr>
<td><em>C. krusei</em></td>
<td>0.25</td>
<td>1</td>
<td>&gt; 32</td>
</tr>
</tbody>
</table>
Statistical analysis

- Chi square test for association.
- Fisher’s exact test.
- Monte Carlo simulation.
- McNemar’s test.
- Cochran-Armitage test for trend.
- Independent sample Student’s $t$ test.
- Wilcoxon-Mann-Whitney test.
- Kruskal-Wallis H test.
- Binomial logistic regression analysis.
- Kaplan-Meier method.
Outline

• Materials and methods
• Results
• Discussion
• Conclusions
Records identified through database searching (n = 163)

Additional records identified through other sources (n = 1)

Additional cases identified through SEI database (n = 32)

Records after duplicates removed (n = 164)

Records screened (n = 164)

Studies assessed for eligibility (n = 164)

Studies included (n = 76)

Cases selected for analysis (n = 111)

Cases included in the review analysis (n = 140)
Slide withheld at request of author
Candida Infective Endocarditis: an Observational Cohort Study with a Focus on Therapy
Arnold et al (ICE group) AAC 2015 early online
ESCMID eLibrary

Slide withheld at request of author
Over time (1965-95), dramatic changes have occurred in the major risk factors for fungal endocarditis.....

Ellis et al, CID 2001
Slide withheld at request of author
Predisposing factors for early onset post cardiosurgery candidemia

- Antibiotics pressure

Selection for *Candida* GI colonization

- Increased intestinal mucosa permeability

Increased chances of *Candida* intestinal translocation

- Other risk factors of ICU patients
  - cvc, NPT, renal failure +/- CRRT,
  - multiple comorbidities……..
# Predisposing factors for candidemia after cardiosurgery

Michalopoulos AS et al *CHEST* 124: 2244, 2003

<table>
<thead>
<tr>
<th>Variabile</th>
<th>OR</th>
<th>P</th>
<th>sens</th>
<th>spec</th>
<th>PPV</th>
<th>NPV</th>
<th>accuratezza</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Candidemia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MV&gt;10 day</td>
<td>28.2</td>
<td>&lt;.001</td>
<td>97%</td>
<td>99%</td>
<td>97%</td>
<td>99%</td>
<td>99%</td>
</tr>
<tr>
<td>Bacterial inf.</td>
<td>9.4</td>
<td>&lt;.001</td>
<td>100%</td>
<td>92%</td>
<td>76%</td>
<td>100%</td>
<td>94%</td>
</tr>
<tr>
<td>CPBP&gt;120 min</td>
<td>8.1</td>
<td>&lt;.01</td>
<td>70%</td>
<td>85%</td>
<td>54%</td>
<td>92%</td>
<td>82%</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2.4</td>
<td>&lt;.01</td>
<td>60%</td>
<td>70%</td>
<td>33%</td>
<td>87%</td>
<td>68%</td>
</tr>
<tr>
<td>Global model</td>
<td></td>
<td></td>
<td>53%</td>
<td>100%</td>
<td>100%</td>
<td>90%</td>
<td>90%</td>
</tr>
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</table>
**S. cerevisiae subspp boulardii** fungemia in a post CCH ICU following assumption of probiotic formulation

Munoz & Bouza CID 2005

<table>
<thead>
<tr>
<th>probiotic</th>
<th>fungemia</th>
<th>no fungemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>yes</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>no</td>
<td>0</td>
<td>38</td>
</tr>
<tr>
<td>total</td>
<td>3</td>
<td>40</td>
</tr>
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Intestinal hypoperfusion

→

*Candida* translocation and candidemia

Sessile progression of pathogenic *Candida*

With biofilm formation

CVC

Valvular prosthesis, Pace-maker
<table>
<thead>
<tr>
<th></th>
<th>no endocarditis (n=33)</th>
<th>endocarditis (n=11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deaths within 1 mo.</td>
<td>53%</td>
<td>9%</td>
</tr>
<tr>
<td>Deaths within 1 year</td>
<td>83%</td>
<td>9%</td>
</tr>
<tr>
<td>surgery/autopsy</td>
<td>27% (9/33)</td>
<td>100%</td>
</tr>
<tr>
<td>Lost to follow up</td>
<td>9% (3/33)</td>
<td>..........</td>
</tr>
</tbody>
</table>

Time lapse from surgery to endocarditis (mean days) 250
Four patients developed an early candidemia after prosthetic valve implantation with no TEE evidences of heart valve involvement.

In a mean time of approximately 380 days these patients were readmitted to the hospital and diagnosed with PVE due to the same fungus detected during the first episode of candidemia.

Persistently elevated serum BDG despite apparent candidemia clearance my corroborate suspicion that postsurgery candidemia is evolving towards late PVE
OPEN HEART SURGERY

RISK FACTORS FOR CANDIDEMIA
(NPT, SEVERE SEPSIS, ANTIBIOTICS, ACUTE RENAL FAILURE, CANDIDA COLONIZATION, STEROIDS ETC)

POST-OPERATIVE CANDIDEMIA*
FROM ECC DAMAGED INTESTINAL MUCOSA
* Frequently undetected for the low sensitivity of blood cultures.

direct intraoperative contamination or unsuccessful antifungal therapy & surgical debridment of previous Candida IE

adherence of Candida on prosthetic valve

biofilm formation

resistance to antifungals, no evidence of IE at echocardiography!

Late appearance of vegetations at echocardiography and/or clinical symptoms of IE

DIAGNOSIS OF CANDIDA PVE

At least 25% of post-operative candidemias develop endocarditis!

Falcone M. & Venditti M et al Medicine 2009
Intestinal hypoperfusion

$\Rightarrow$

*Candida* translocation and candidemia

- **CVC**
- Sessile progression of pathogenic *Candida*
- With biofilm formation

- **Valvular prosthesis**
Slide withheld at request of author
Candida PVE is a biofilm formation dependent process that progresses as slowly as much is the presence of non biological material on prosthetic valves

1. While bioprosthetic materials allow the development of thrombotic vegetations with fungal biofilm in them, mechanical prostheses, which lack of any biological component, do not sustain fungal growth…


2. The mechanism of candidal infection and biofilm forming on mechanical prosthetic valve is related to the presence of a neoendocardium rather than to the sewing cloth or metallic substances of the valve itself.


3. Neoendocardium and neoendothelization on mechanical protheses are processes that may vary from 3 to 10 months up to 18 to 24 months.

What about therapy?
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Antifungal Combinations against Simulated *Candida albicans* Endocardial Vegetations

Candida Infective Endocarditis: an Observational Cohort Study with a Focus on Therapy

Arnold CJ et al Antimicrob Agents Chemother 2015 early on line

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Overall treatment subgroup (n = 33)</th>
<th>Amphotericin B group (n = 11)</th>
<th>Echinocandin group (n = 14)</th>
<th>P&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Community acquired</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 (31)</td>
<td>9 (82)</td>
<td>6 (42)</td>
<td></td>
<td>0.05</td>
</tr>
<tr>
<td><strong>Age (yr)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (95% CI)</td>
<td>61.0 (55.5–66.4)</td>
<td>52.4 (43.4–61.3)</td>
<td>62.5 (52.6–72.4)</td>
<td>0.12</td>
</tr>
<tr>
<td>≥50</td>
<td>26 (79)</td>
<td>8 (73)</td>
<td>10 (71)</td>
<td>1.00</td>
</tr>
<tr>
<td>≥60</td>
<td>19 (58)</td>
<td>3 (27)</td>
<td>10 (71)</td>
<td>0.05</td>
</tr>
<tr>
<td>≥70</td>
<td>14 (42)</td>
<td>1 (9)</td>
<td>7 (50)</td>
<td>0.04</td>
</tr>
<tr>
<td><strong>Mortality</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In hospital</td>
<td>13 (39)</td>
<td>5 (45)</td>
<td>4 (29)</td>
<td>0.43</td>
</tr>
<tr>
<td>42 days</td>
<td>14 (42)</td>
<td>5 (45)</td>
<td>5 (36)</td>
<td>0.62</td>
</tr>
<tr>
<td>1 yr</td>
<td>21 (66)</td>
<td>7 (64)</td>
<td>9 (69)</td>
<td>1.00</td>
</tr>
</tbody>
</table>

No differences in risk factors, complications (stroke, heart failure, embolization), echo findings, Candida spp distribution, surgical therapy, combo rx, and chronic suppressive rx.
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Both NVE and PVE could be considered biofilm-related diseases with common pathogenetic pathways characterized, perhaps in the majority of cases, by intestinal translocation of Candida spp. and initial transient candidemia.

2. This early fungal bloodstream infection, that might even pass clinically unnoticed, might be followed by fungal colonization of the valve and subsequent biofilm formation.

3. The importance of biofilm formation is even higher in PVE in which the type of prosthesis play a noteworthy role in time to disease onset and anti-biofilm agent have a considerable impact in reducing mortality.

4. Cardiac surgery, initial EAB & chronic suppressive antifungal therapy might be crucial therapeutic interventions with the potential to increase patient survival.

5. Shorter times to diagnosis might have a role in reducing mortality with TEE performing better than TTE examination in the diagnostic algorithm.
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