Candida and other yeast infections in children: epidemiology data and diagnostic options

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Disclosure

- I’m adviser for Pfizer, Merck
Candida and other yeasts in children?

Epidemiology

Diagnostic options
Agenda

- Why epidemiology is so important in 2018?
- How often in this infection in children population?
- Is there any difference in regard to adult population?
- Diagnostic options:
  - what do we have?
  - What do we have that is really good for children?
  - Are we satisfied with what we have?
Agenda

- Why epidemiology is so important in 2018?
  - IFD in children is affected by geographical, population and time variability
  - Epidemiological data direct preventive, diagnostic and therapeutic
Why epidemiology in 2018

Prophylaxis – empirical – preemptive therapy

Long-term exposure to antifungal agents

CVC – non linear PK of certain antifungal agents – neutropenia – intense immunosuppression

Widespread use of agricultural and industrial fungicides with similar chemical structures and mechanisms of action
Agenda

- Why epidemiology is so important in 2018?
- **How often in this infection in children population?**
- Is there any difference in regard to adult population?
- **Diagnostic options:**
  - what do we have?
  - What do we have that is really good for children?
  - Are we satisfied with what we have?
Candidiasis in children and Neonates: Who are the patients at risk?

Infants and Children
- Immunosuppression
- Use of broad-spectrum antibiotics
- Central venous catheter
- Abdominal surgery/perforation
- Hyperalimentation
- Hemodialysis

Neonates
- Prematurity and birth weight
- Abdominal surgery
- NEC
- Exposure to broad-spectrum antibacterial agents
- Parenteral nutrition
- H2 blockers
- Intubation
### Tabela 03 - Distribuição dos microrganismos notificados como agentes etiológicos de IPCS em pacientes hospitalizados em UTI adulto (Brasil, 2015)

<table>
<thead>
<tr>
<th>Ordem de frequência</th>
<th>Microrganismos</th>
<th>Número</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;a&lt;/sup&gt;</td>
<td><em>K. pneumoniae</em></td>
<td>3.805</td>
<td>16,9</td>
</tr>
<tr>
<td>2&lt;sup&gt;a&lt;/sup&gt;</td>
<td>SCoN</td>
<td>3.703</td>
<td>16,5</td>
</tr>
<tr>
<td>3&lt;sup&gt;a&lt;/sup&gt;</td>
<td><em>Staphylococcus aureus</em></td>
<td>2.959</td>
<td>13,2</td>
</tr>
<tr>
<td>4&lt;sup&gt;a&lt;/sup&gt;</td>
<td><em>Acinetobacter spp.</em></td>
<td>2.734</td>
<td>12,2</td>
</tr>
<tr>
<td>5&lt;sup&gt;a&lt;/sup&gt;</td>
<td><em>P. aeruginosa</em></td>
<td>2.242</td>
<td>10,0</td>
</tr>
<tr>
<td>2&lt;sup&gt;a&lt;/sup&gt;</td>
<td><strong>Candida spp.</strong></td>
<td>1.711</td>
<td>7,6</td>
</tr>
<tr>
<td>7&lt;sup&gt;a&lt;/sup&gt;</td>
<td><em>E. coli</em></td>
<td>1.631</td>
<td>7,2</td>
</tr>
<tr>
<td>8&lt;sup&gt;a&lt;/sup&gt;</td>
<td><em>Enterococcus spp.</em></td>
<td>1.226</td>
<td>5,4</td>
</tr>
<tr>
<td>9&lt;sup&gt;a&lt;/sup&gt;</td>
<td><em>Enterobacter spp.</em></td>
<td>1.089</td>
<td>4,8</td>
</tr>
<tr>
<td>10&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Outras enterobactérias</td>
<td>856</td>
<td>3,8</td>
</tr>
<tr>
<td>11&lt;sup&gt;a&lt;/sup&gt;</td>
<td><em>Serratia spp.</em></td>
<td>543</td>
<td>2,4</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td></td>
<td>22.499</td>
<td>100,0</td>
</tr>
</tbody>
</table>

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<sup>a</sup> Identificação bacteriana realizada de acordo com a metodologia disponível em cada serviço de saúde.

<sup>1</sup> Candida albicans (951) e Candida não-albicans (760).

<sup>2</sup> E. faecalis (601), E. faecium (251) e Enterococcus spp. (374).

<sup>3</sup> Enterobactérias identificadas como pertencentes ao gênero Citrobacter spp., Proteus spp. ou Morganella spp.

Fonte: GVIMS/GGTES/ANVISA, 2016.
### Tabela 05 – Distribuição dos microrganismos notificados como agentes etiológicos de IPCSL associada a CVC em pacientes pediátricos hospitalizados em UTIs (Brasil, 2015).

<table>
<thead>
<tr>
<th>Ordem de frequência</th>
<th>Microrganismos</th>
<th>Número</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1ª</td>
<td>SCoN</td>
<td>456</td>
<td>19,8</td>
</tr>
<tr>
<td>2ª</td>
<td>K. pneumoniae</td>
<td>407</td>
<td>17,7</td>
</tr>
<tr>
<td>3ª</td>
<td>*Candida spp.*¹</td>
<td>336</td>
<td>14,6</td>
</tr>
<tr>
<td>4ª</td>
<td><em>Staphylococcus aureus</em></td>
<td>268</td>
<td>11,7</td>
</tr>
<tr>
<td>5ª</td>
<td>P. aeruginosa</td>
<td>227</td>
<td>9,9</td>
</tr>
<tr>
<td>6ª</td>
<td>**Enterobacter spp.**³</td>
<td>170</td>
<td>7,4</td>
</tr>
<tr>
<td>7ª</td>
<td>Acinetobacter spp.</td>
<td>114</td>
<td>5,0</td>
</tr>
<tr>
<td>8ª</td>
<td>**Enterococcus spp.**²</td>
<td>104</td>
<td>4,5</td>
</tr>
<tr>
<td>9ª</td>
<td><em>Serratia spp.</em></td>
<td>97</td>
<td>4,2</td>
</tr>
<tr>
<td>10ª</td>
<td>E. coli</td>
<td>69</td>
<td>3,0</td>
</tr>
<tr>
<td>11ª</td>
<td>Outras enterobactérias</td>
<td>50</td>
<td>2,2</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td></td>
<td>2298</td>
<td>100,0</td>
</tr>
</tbody>
</table>

¹Identificação bacteriana realizada de acordo com a metodologia disponível em cada serviço de saúde.
²Candida albicans (134) e Candida não-albicans (202).
³E. faecalis (53), E. faecium (17) e Enterococcus spp. (37).

Fonte: GViMS/GGTES/ANVISA, 2016.
Tabela 07 – Distribuição dos microrganismos notificados como agentes etiológicos de IPCSL relacionada a CVC em pacientes neonatos hospitalizados em UTIs (Brasil, 2015).

<table>
<thead>
<tr>
<th>Ordem de frequência</th>
<th>Microrganismos</th>
<th>Número</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1ª</td>
<td>SCcoN</td>
<td>2.400</td>
<td>34,6</td>
</tr>
<tr>
<td>2ª</td>
<td>K. pneumoniae</td>
<td>1.125</td>
<td>16,2</td>
</tr>
<tr>
<td>3ª</td>
<td><em>Candida</em> spp.</td>
<td>761</td>
<td>11,0</td>
</tr>
<tr>
<td>4ª</td>
<td>Staphylococcus aureus</td>
<td>697</td>
<td>10,0</td>
</tr>
<tr>
<td>5ª</td>
<td>Enterobacter spp.</td>
<td>587</td>
<td>8,5</td>
</tr>
<tr>
<td>6ª</td>
<td>E. coli</td>
<td>275</td>
<td>4,0</td>
</tr>
<tr>
<td>7ª</td>
<td>Enterococcus spp.</td>
<td>262</td>
<td>3,8</td>
</tr>
<tr>
<td>8ª</td>
<td>P. aeruginosa</td>
<td>249</td>
<td>3,6</td>
</tr>
<tr>
<td>9ª</td>
<td>Serratia spp.</td>
<td>217</td>
<td>3,1</td>
</tr>
<tr>
<td>10ª</td>
<td>Acinetobacter spp.</td>
<td>204</td>
<td>2,9</td>
</tr>
<tr>
<td>11ª</td>
<td>Outras enterobactérias</td>
<td>161</td>
<td>2,3</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td></td>
<td>6.938</td>
<td>100,0</td>
</tr>
</tbody>
</table>

a. Identificação bacteriana realizada de acordo com a metodologia disponível em cada serviço de saúde.

*Candida albicans* (338) e *Candida não-albicans* (423).

*E. faecalis* (160), *E. faecium* (10) e Enterococcus spp. (92).

Enterobactérias identificadas como pertencentes ao gênero *Citrobacter* spp., *Proteus* spp. ou *Morganella* spp.


Benjamin DK, Pediatrics, 2003
THE INCIDENCE OF CANDIDIASIS TENDS TO INCREASE WORLDWIDE!

Logical conclusion...
How is The incidence of Candidiasis worldwide in Children Population?

- A) tends to decrease
- B) tends to increase
- C) we have no good data on that
- D) I have no idea about the “E.T.” epidemiology...
The incidence of candidiasis tends to INCREASE worldwide!

Logical conclusion...
Decreasing Rates of Invasive Candidiasis in Pediatric Hospitals Across the United States


Clinical Infectious Diseases, Volume 58, Issue 1, 1 January 2014, Pages 74–77,
Supplementary Figure 1. Crude rate of invasive candidiasis as cases per 10,000 inpatient days and percent of patients receiving fluconazole prophylaxis, 2003 to 2011

How to explain?
Better general measures?
Decrease of BSI rate?
Better ATB use?
Fluco prophylaxis?

Includes neonatal admissions, <1500 grams and admitted to PHIS institution on day of or one day after birth.
Candidemia Incidence over the last 12 y – NCIU – São Paulo – Brazil - ELBW
Invasive fungal disease in children (yeast): who is the "leader"?
Invasive fungal disease in children (Yeast): who is the “leader”? 

An epidemic of Malassezia pachydermatis in an intensive care nursery associated with colonization of health care workers' pet dogs.


15 infants

Source?

Pana ZD, 2017
Zaoutis TE, 2006
Raymond J, 2000
What about other yeasts in Children

- *Rhodotorula mucilaginosa*
- fungal cutaneous infection in immunocompromised child (retinoblastoma)

Fluconazol and ketoconazol showed susceptibles

*J Mycol Med.* 2018 Mar 15
IC incidence pediatric studies

4.3/10,000 ped admissions
US

<1y 11/100,000 person y
10-14y 0.47/100,000 person y
England & Wales

ATL 13.3/100,000 person y
BTM 26.6/100,000 person y

ATL 29%
BTM 28%

Mortality

10% children
22% neonates

15.8%

4.6/10,000 admissions
Australia

8.1/10,000 ped admissions
LA

Zaoutis et al, Santolaya et al, Oeser et al, Blyth et al, Cleveland et al, Pana ZD et al

NR

© by author
Distribution of *Candida spp*. Causing IFD in Children

US /IPFN– International Pediatric Fungal Network
Non albicans *Candida spp*
Ped: 56%
Neo: 52%

AUSTRALIA
*Candida parapsilosis*
Ped: 38%
Neo: 42%

Latin America
Non albicans *Candida spp*
Ped: 56.2% (*C. parap* 27%)
Neo: 64.3% (*C parap* 26.3%)

Zaoutis et al, Santolaya et al, Blyth et al, Pana ZD et al
Species Distribution of 302 Episodes of Candidemia in Neonates and Children from Latin America (23 hospitals, 8 countries)

<table>
<thead>
<tr>
<th>Species</th>
<th>N</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C. albicans</td>
<td>76</td>
<td>35.7</td>
</tr>
<tr>
<td>C. parapsilosis</td>
<td>56</td>
<td>26.3</td>
</tr>
<tr>
<td>C. lusitaniae</td>
<td>31</td>
<td>14.6</td>
</tr>
<tr>
<td>Other Candida</td>
<td>27</td>
<td>12.7*</td>
</tr>
<tr>
<td>Other Non-Candida</td>
<td>7</td>
<td>3.3</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>2.3</td>
</tr>
<tr>
<td></td>
<td>11</td>
<td>5.1</td>
</tr>
</tbody>
</table>

* P value nonsignificant for all species except for C. glabrata and C. krusei.
† Other Candida species were identified but not further specified.

Mortality risk: C. albicans X C. parapsilosis

Australia (2017)
26.7%
42%
X
20%
P<.001

Benjamin D, Stoll B, Fanaroff AA. Pediatrics, 2006;117:84-92

Chapman B, J Antimicrob Chemother 2017
All isolates of *C. albicans*, *C. parapsilosis* and *C. tropicalis* (N = 239) were susceptible to fluconazole, with the exception of 1 *C. parapsilosis* isolate, which was SDD.

Of 10 isolates of *C. glabrata*, 9 were SDD and 1 was resistant.

For anidulafungin, there was 1 *C. tropicalis* isolate (2.3%) with intermediate susceptibility.
Candida sp were the most common pathogens isolated:

- *C. albicans* 170 (59.4%)
- *C. parapsilosis* 59 (20.6%) of cases
- 6 cases of *C.lusitaeniae* (2.1%)
- 6 cases (2.1%) *C. glabrata*
Even looking carefully ... the diagnosis of candida infection is not easy ...
Diagnostic Options for *Candida*: which diagnostic method is the regular one at your hospital?

- 1) PCR
- 2) Blood Culture automated method
- 3) T2 Candida Magnetic Resonance or MALDI–TOF
- 4) β–D Glucan
- 5) Combination of methods from above
- 6) No lab diagnostic, just “intuition”
Are you satisfied with the diagnostic method available in your hospital?

- 1) fully satisfied
- 2) yes, but it could be better
- 3) no, I’m afraid I’m not performing diagnostic of candidiasis in childrens...
- 4) My dream of consumption is the T2 Candida Magnetic Resonance
- 5) more than one alternative is correct
Diagnosis of Invasive Candidiasis

• Obstacles
  – Signs and symptoms may be non-specific
  – Blood cultures for Candida
    • < 10% positive in patients with hepatosplenic candidiasis
    • 60 – 80% positive in patients with 2 or more organs involved at autopsy
  – Invasive procedures risky and difficult
  – Need for sensitive minimally invasive strategies

• Benefit
  – Early and appropriate intervention decreases mortality
Very limited data in children:
  ◦ Elevated levels of BG were reported in 4 children with IFD (3 patients with candidemia, 1 patient with probable aspergillosis)
  ◦ Mean BG levels are higher in immunocompetent uninfected children than adults: optimal cut-off children
Cohort study of 130 pediatric patients
  ◦ Malignancy (89 hematologic, 11 other)
  ◦ Critically ill at high risk (30)
  ◦ Twice-week sampling using GKT-5M assay
  ◦ Sensitivity 82% and specificity 82%
BG in neonates

- Retrospective study in Amiens University Medical Center
- BG assay performed on newborns suspected to have candidiasis
- 18 infected; 43 uninfected
- BG higher in infected (364 pg/ml) vs 89 pg/ml in uninfected (p <0.001)
- Cutoff of 125 pg/ml had 84% sensitivity and 75% specificity

Decrease in the serum (1–3)-β-d-glucan levels (pg/ml) over the course of 21 days antifungal therapy in infected patients (log-transformed variable).
Role of serum 1,3β-d-glucan assay in early diagnosis of invasive fungal infections in a neonatal intensive care unit.

Shabaan AE¹, Elbaz LM², El-Emshaty WM³, Shouman B⁴.

92 infants were eligible for the study

- 15 infants were excluded
  - Parents refused (N=7)
  - Haemolysed samples (N=4)
  - Insufficient sample (N=4)

77 infants were included

Classified according blood culture

No Fungemia (N=41)
- Culture growing Bacteria

Suspected fungemia (N=25)
- No growth by culture

Definite fungemia (N=11)
- Culture growing Candida

Figure 1  Study flowchart.
BG in neonates

Limitations: small sample size and use of blood culture as a gold standard for diagnosis of IFD

Cut off value of 95 pg/mL
(manufacturer):
S: 63.6%
Sp:90.2%
PPV:63.6%
NPV:90.2%
Accuracy of the BG assay: 84.6%

BEST Cut-off value of 99 pg/mL:
S: 63.6%
Sp:95.1%
PPV:77.8%
NPV:90.7%
Accuracy of the BG assay: 88.5%

Figure 2 1,3-β-D-glucan levels in studied neonates.
Observational multicenter (17) case control study

The performance of serum BDG and Candida PCR (blood/serum/sterile samples) x culture


- 159 episodes
- 9 IC (7 confirmed/2 probably)
- IC prevalence: 5.7%
- Mortality: IC=44.4% x non-IC episodes=11.1% (p < 0.01)

**TABLE 8 Diagnostic accuracy of PCR and BDG in all samples analyzed**

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>No. of samples (%) sensitivity (n = 8)</th>
<th>No. of samples (%) specificity (n = 103)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCR blood/serum</td>
<td>7 (87.5)</td>
<td>84 (81.6)</td>
<td>26.9</td>
<td>98.8</td>
</tr>
<tr>
<td>Positive BDG (&gt;80 pg/ml)</td>
<td>6 (75.0)</td>
<td>66 (64.6)</td>
<td>14.0</td>
<td>97.1</td>
</tr>
<tr>
<td>Positive BDG (&gt;120 pg/ml)</td>
<td>6 (75.0)</td>
<td>70 (68.0)</td>
<td>15.4</td>
<td>97.2</td>
</tr>
<tr>
<td>Positive PCR or BDG</td>
<td>7 (87.5)</td>
<td>49 (47.6)</td>
<td>11.5</td>
<td>98.0</td>
</tr>
<tr>
<td>Positive PCR and BDG</td>
<td>6 (75.0)</td>
<td>89 (86.4)</td>
<td>30.0</td>
<td>97.8</td>
</tr>
</tbody>
</table>

*BDG, beta-D-glucan; NPV, negative predictive value; PPV, positive predictive value.

< 1,250g
Both biomarkers offered an attractive method for early diagnosis of IC and might be help rule out IC and minimize the inappropriate use of antifungal compounds.
Current Workflows for Species-Specific Result

- **Blood Culture**: 2-5 days to result
- **Whole blood collection**: 3-5 hours to result

Species Identification (PCR, MALDI-TOF, FilmArray, Verigene) REQUIRES POSITIVE BLOOD CULTURE

- **Species Specific Pathogen Detection**: Enables Targeted Therapy

40-50% of *Candida* infections are missed by blood culture¹

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Speed and Accuracy of T2

**T2CANDIDA SPEED**

- **AVERAGE TIME TO RESULTS**
  - **POSITIVE (WITH SPECIES ID)**
    - T2CANDIDA: 4.4 HRS
    - **BLOOD CULTURE**: 129 HRS
  - **NEGATIVE**
    - T2CANDIDA: 4.2 HRS
    - **BLOOD CULTURE**: ≥ 120 HRS

**T2CANDIDA ACCURACY**

- **96.4%** Sensitivity
- **99.4%** Specificity

**Clinical Benefits**

- Mortality
- Cost
- Resistance
- Length of stay
- Toxicity Risk

Blood culture demonstrates a sensitivity of 50-60%
# T2Candida in Pediatric Samples

<table>
<thead>
<tr>
<th>Blood Culture</th>
<th>C. albicans/trop</th>
<th>C. parapsilosis</th>
<th>C. glabrata</th>
<th>Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>C. parapsilosis</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>C. albicans</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>C. glabrata</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>C. tropicalis</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Negative</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>9</td>
</tr>
</tbody>
</table>

**TIME THERAPY UNNECESSARY ANTIFUNGAL USE**

Lower volumes used compared to adults approx. 2 ml

1 mL from Newborn = 70 ml from adult patient

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PRE X POST T2 Candida implementation

TIME TO APPROPRIATE THERAPY:
- 34h x 6h  \( p = 0.0147 \)

EMPIRICAL ANTIFUNGAL THERAPY AVOIDED FOR T2 Candida NEGATIVE PATIENT: 58.4%

No children at the study
In Conclusion:
Surveillance of Yeast infection is still crucial for defining clinical management of children's infections.
Admit that you can not always diagnose yeast, but treat as if it were true! And on time!