Treatment of invasive fungal infections in immunocompromised patients
Experience with Anidulafungin

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Issues to be addressed

- Epidemiology and risk factors
- Strategies – prophylaxis, empirical, preemptive, targeted
- UHC Zagreb – epidemiology, approach to invasive fungal infections
- Why anidulafungin? When and how?
- Conclusions
Any fungal species found in nature can cause infection if the host is immunocompromised
Who are patients at high risk?
Broad Spectrum of Patients

<table>
<thead>
<tr>
<th>Non-Neutropenic</th>
<th>Neutropenic</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Acute renal failure</td>
<td>• Cancer</td>
</tr>
<tr>
<td>• Parenteral nutrition</td>
<td>• Transplantation</td>
</tr>
<tr>
<td>• Anti-anaerobic agents</td>
<td>• Broad-spectrum anti-anaerobic antibiotic use</td>
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<tr>
<td>• Prior vancomycin use</td>
<td>• Prior vancomycin use</td>
</tr>
<tr>
<td>• Intralipid agents</td>
<td>• Immunocompromised state</td>
</tr>
<tr>
<td>• Prior surgery</td>
<td>• Surgery</td>
</tr>
<tr>
<td>• Indwelling triple-lumen catheters</td>
<td>• Indwelling catheters</td>
</tr>
</tbody>
</table>


National Epidemiology of Mycosis Survey (NEMIS) was a prospective, multicenter study conducted at 6 US sites from 1993-1995 to examine rates of risk factors for the development of candidal bloodstream infections (CBSIs) among patients in surgical and neonatal ICUs >48h. Among 4276 patients, 42 CBSIs occurred.
What is important in antifungal treatment
Late intervention negatively influences survival

Mortality of high risk patients with invasive aspergillosis

Delay of treatment in high risk patients doubled mortality from IA

Treatment delay leads to greater fungal burden which negatively affects treatment outcome

- Antifungal treatment started \( \leq 10 \) days after start of pneumonia
- Antifungal treatment started \( >10 \) days after start of pneumonia

Increased mortality due to inadequate antifungal therapy

- *Candida* and VRE accounted for the majority of inadequate antimicrobial treatments
- Inadequate antimicrobial treatment was found to be the most important independent determinant of hospital mortality for the entire patient cohort*

* Inadequate antimicrobial treatment included the absence of therapy for fungemia due to *Candida albicans*

<table>
<thead>
<tr>
<th>TIME OF THERAPY</th>
<th>CHOICE OF THE MOST EFFICIENT AND SAFE DRUG</th>
</tr>
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</table>

**APPROPRIATE ANTIFUNGAL THERAPY**

SUCCESS OF THERAPY

EARLY DIAGNOSIS
APPROPRIATE ANTIFUNGAL THERAPY

TIME OF THERAPY

CHOICE OF THE MOST EFFICIENT AND SAFE DRUG

APPROPRIATE DOSING (resorbed!)

SUSCEPTIBILITY / RESISTANCE COMBINATIONS!

LOCAL EPIDEMIOLOGY

SOURCE OF INFECTION (local situation)

EARLY DIAGNOSIS

SUCCESS OF THERAPY

IMMUNE STATUS OF THE HOST!
DIAGNOSTIC DIFFICULTIES IN FUNGAL INFECTIONS

- Which tests is reliable enough?
- Clinical symptoms not characteristic
- Current standard of relying on culture based detection of filamentous fungi is not adequate
- Manifestations on imaging seldom specific
- Biopsy often impossible
- Serologic tests not universally available
What strategies we use? When and how?

Risk of infection

Infection

Disease

**Prophylaxis**
- Diagnosis driven – positive test

**Empirical**
- Beta-D-glucan

**Pre-emptive**
- Nucleic acids
- Galactomannan

**Specific therapy**
Empirical therapy: definition

- Prolonged, profound neutropenia
- Persisting fever (4-7 days) of uncertain origin refractory to broad-spectrum antibiotic treatment
- Invasive fungal disease cannot be ruled out

High-risk, febrile but no evidence of IFD
Why we still use empirical antifungal therapy?

- High incidence and fatality rates for invasive fungal infections
- Insufficient diagnostics
  - Culture-based methods
    - Helpful only with *Candida*
    - Rarely diagnostic for invasive Aspergillus infections
- Late treatment greatly reduces success rates
- Many invasive fungal infections are diagnosed too late or only at autopsy
Pre-emptive or diagnostics-driven therapy

initiated for when invasive fungal disease is likely

- **clinical evidence** *eg* halo sign
  
  OR

- **mycological evidence**

  *eg* *Aspergillus* galactomannan detected in plasma

High-risk and some evidence of IFD
Approach to antifungal strategies for patients at risk of acquiring IFI

Starting point – risk assessment

Low risk

Population at risk for IFD

High risk

Local epidemiology
HEPA

Preventative strategy

No prophylaxis

Fluconazole prophylaxis

Mould-active prophylaxis

Empirical

Diagnostic driven

Empirical

Diagnostic driven

Empirical

Diagnostic driven

Empirical

Diagnostic driven

Empirical

Diagnostic driven

No diagnostic facilities available

Use only to buy time until IFD is confirmed or excluded

Screening tests implemented

Results same/next day

CT-scan accessible

Bronchoscopy available
How we use antifungal drugs
Division of Hematology, UHC Zagreb

• Fluconazole - prophylaxis, low risk patients, therapy – very rare
• Posaconazole – prophylaxis, high risk patients, therapy – occasionally (combination)
• Lipid formulations of Amphotericin B – therapy, unknown causative agent, pulmonary infiltrate undiagnosed, multirezistant agent, galactomannan negative
• Voriconazole – aspergillus, pulmonary infiltrate, galactomannan positive
• Caspofungin – empirical therapy of prolonged fever, Candida
• Anidulafungin – Candida, empirical therapy for prolonged fever
• Mycafungin – prophylaxis in selected patients, Candida
• Why anidulafungin?
Anidulafungin Molecular Structure is Different From the Other Echinocandins

- Greater volume of distribution
- More potent antifungal activity
- Longer half-life
- No hepatic metabolism
- No known drug interactions
- No dose adjustments in hepatic or renal insufficiency

Unique lipophilic side chain

- Greater volume of distribution
- More potent antifungal activity
**ECALTA®**
Easy to administer with convenient/simple dosing

| Simple dosing<sup>1</sup> | 200 mg loading dose on day 1  
<table>
<thead>
<tr>
<th></th>
<th>100 mg daily thereafter</th>
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<table>
<thead>
<tr>
<th></th>
<th></th>
<th>Special populations:&lt;sup&gt;1&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatic impairment</td>
<td><strong>No dose adjustments</strong> required for patients with mild, moderate, or severe hepatic impairment</td>
<td></td>
</tr>
<tr>
<td>Renal impairment</td>
<td><strong>No dose adjustments</strong> required for patients with any degree of renal insufficiency, including those on dialysis</td>
<td></td>
</tr>
<tr>
<td>Other special populations</td>
<td><strong>No dose adjustments</strong> required based on gender, weight, ethnicity, HIV positivity, or geriatric status</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drug interactions&lt;sup&gt;1&lt;/sup&gt;</th>
<th><strong>No known drug interactions to consider</strong></th>
</tr>
</thead>
</table>

What we are doing in UHC Zagreb?
Number of newly diagnosed acute leukemia patients 2011-2013

Number of newly diagnosed acute leukemia patients 2011-2013

- 2011: 37
- 2012: 52
- 2013: 58

Bar chart showing the number of newly diagnosed acute leukemia patients from 2011 to 2013.
No of allogeneic SCT by year
Hematology UHC Zagreb

N=954

520

434
No of allogeneic SCT according to year and donor
Hematology UHC Zagreb

High risk for IFI!
No od allogeneic SCT according to year and intensity of conditioning

Hematology UHC Zagreb

High risk for IFI!
Autologous stem cell transplantation 1988-2015, UHC Zagreb

N=1568
Epidemiology - Invasive fungal infections
Division of Hematology UHC Zagreb, IFI N=197

Patients with invasive infection:

- Yeasts : molds (40 : 60)%
  - *C. albicans* : *Candida* spp. (38:62)%
  - *Aspergillus* : non-*Aspergillus* (91:9)%

M. Jandrlić 2008.
Distribution of yeast isolates, UHC Zagreb (total, not only hematology) 
N = 24,031

- Candida albicans: 44%
- Candida glabrata: 15%
- Candida dubliniensis: 14%
- Candida parapsilosis: 7%
- Candida krusei: 6%
- Saccharomyces cerevisiae: 3%
- Candida tropicalis: 2%
- Candida kefyr: 2%
- Druge Candida: 7%
Division of hematology, UHC Zagreb, N=110

### 1993-2001. (12/year)

- **N=110**

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<table>
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<tbody>
<tr>
<td><strong>%</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C. albicans</td>
<td>31.4</td>
<td></td>
</tr>
<tr>
<td>C. parapsilosis</td>
<td>18.6</td>
<td></td>
</tr>
<tr>
<td>C. krusei</td>
<td>9.8</td>
<td></td>
</tr>
<tr>
<td>Trichosporon spp.</td>
<td>8.8</td>
<td></td>
</tr>
<tr>
<td>C. guillermondii</td>
<td>6.9</td>
<td></td>
</tr>
<tr>
<td>C. glabrata</td>
<td>5.9</td>
<td></td>
</tr>
<tr>
<td>C. tropicalis</td>
<td>5.9</td>
<td></td>
</tr>
<tr>
<td>Cryptococcus neof.</td>
<td>3.9</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>8</td>
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</table>

#### Mortality 53.7%

### 2006-2008. (5/year)

- **N=15**

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<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td><strong>%</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C. krusei</td>
<td>26.7</td>
<td></td>
</tr>
<tr>
<td>C. parapsilosis</td>
<td>20.0</td>
<td></td>
</tr>
<tr>
<td>C. tropicalis</td>
<td>13.3</td>
<td></td>
</tr>
<tr>
<td>C. dubliniensis</td>
<td>6.7</td>
<td></td>
</tr>
<tr>
<td>C. glabrata</td>
<td>6.7</td>
<td></td>
</tr>
<tr>
<td>Trichosporon sp.</td>
<td>6.7</td>
<td></td>
</tr>
<tr>
<td>Geotrichum capit.</td>
<td>6.7</td>
<td></td>
</tr>
<tr>
<td>Geotrichum clav.</td>
<td>6.7</td>
<td></td>
</tr>
<tr>
<td>Paecylomyces sp.</td>
<td>6.7</td>
<td></td>
</tr>
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</table>

#### Overall mortality 27%

Atributive mortality 7%
**Local epidemiology**

*In vitro* sensitivity of *Candida* to fluconazole.

<table>
<thead>
<tr>
<th>Antifungal agent</th>
<th>N FKZ</th>
<th>≤8</th>
<th>4, 8</th>
<th>16-32</th>
<th>≥64</th>
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<tbody>
<tr>
<td>MIC sensitivity %</td>
<td></td>
<td>S</td>
<td>—</td>
<td>SDD</td>
<td>R</td>
</tr>
<tr>
<td>C.glabrata**</td>
<td>298</td>
<td>70.1</td>
<td>50.7</td>
<td>19.1</td>
<td>10.7</td>
</tr>
<tr>
<td>C.albicans</td>
<td>114</td>
<td>99.1</td>
<td>5.3</td>
<td>0.9</td>
<td>0</td>
</tr>
<tr>
<td>C.krusei</td>
<td>84</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>C.parapsilosis</td>
<td>55</td>
<td>89.1</td>
<td>0</td>
<td>10.9</td>
<td>0</td>
</tr>
<tr>
<td>C.dubliniensis</td>
<td>30</td>
<td>100</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>C.utilis</td>
<td>30</td>
<td>90</td>
<td>6.7</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>C.pelliculosa</td>
<td>8</td>
<td>75</td>
<td>0</td>
<td>25</td>
<td>0</td>
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<tr>
<td>C.guillermondii</td>
<td>28</td>
<td>75</td>
<td>25</td>
<td>7.1</td>
<td>17.9</td>
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<tr>
<td>C.tropicalis</td>
<td>25</td>
<td>88</td>
<td>12</td>
<td>4</td>
<td>8</td>
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<td>C.kefyr</td>
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<td>90.9</td>
<td>0</td>
<td>9.1</td>
<td>0</td>
</tr>
<tr>
<td>C.lusitaniae</td>
<td>22</td>
<td>100</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

* MIC 4-8 mcg/ml C.glabrata is within limits sensitive. Requires will be treated only with high dose fluconazole. Emergency from the development of resistance.

** Resistances develop relatively quickly (through several hours or days) if was treated with low doses fluconazole.

M. Jandrlić 2013.
**In vitro sensitivity of Candida to voriconazole.**

<table>
<thead>
<tr>
<th>Antifungal agent</th>
<th>N VOR</th>
<th>≤0.06-1</th>
<th>2</th>
<th>≥4</th>
<th>MIC sensitivity %</th>
<th>mic 50</th>
<th>mic 90</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>S</td>
<td>SDD</td>
<td>R</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>C. glabrata</td>
<td>298</td>
<td>84.2</td>
<td>4.7</td>
<td>11.1</td>
<td>0.25</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>C. albicans</td>
<td>114</td>
<td>100</td>
<td>0</td>
<td>0</td>
<td>0.06</td>
<td>0.125</td>
<td></td>
</tr>
<tr>
<td>C. krusei</td>
<td>84</td>
<td>81</td>
<td>16.7</td>
<td>2.4</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>C. parapsilosis</td>
<td>55</td>
<td>96.4</td>
<td>3.6</td>
<td>0</td>
<td>0.06</td>
<td>1</td>
<td></td>
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<tr>
<td>C. dubliniensis</td>
<td>30</td>
<td>100</td>
<td>0</td>
<td>0</td>
<td>0.06</td>
<td>0.06</td>
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<tr>
<td>C. utilis</td>
<td>30</td>
<td>100</td>
<td>0</td>
<td>0</td>
<td>0.125</td>
<td>0.5</td>
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<tr>
<td>C. pelliculosa</td>
<td>8</td>
<td>100</td>
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<td>0</td>
<td>0.25</td>
<td>0.5</td>
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<tr>
<td>C. guillermondii</td>
<td>28</td>
<td>85.7</td>
<td>7.1</td>
<td>7.1</td>
<td>0.06</td>
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<td>C. tropicalis</td>
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<td>92</td>
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<td>8</td>
<td>0.06</td>
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<td>C. kefyr</td>
<td>22</td>
<td>100</td>
<td>0</td>
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<td>0.06</td>
<td>0.125</td>
<td></td>
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<tr>
<td>C. lusitaniae</td>
<td>22</td>
<td>100</td>
<td>0</td>
<td>0</td>
<td>0.06</td>
<td>0.125</td>
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</table>

M. Jandrlić 2013.
### In vitro sensitivity of Candida on amphotericine B.

<table>
<thead>
<tr>
<th>Antifungal agent</th>
<th>N</th>
<th>MIC sensitivity %</th>
<th>≤0.5-1</th>
<th>2</th>
<th>≥4</th>
<th>mic 50</th>
<th>mic 90</th>
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<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C. glabrata</td>
<td>298</td>
<td></td>
<td>99.3</td>
<td>0.8</td>
<td>0</td>
<td>0.5</td>
<td>1</td>
</tr>
<tr>
<td>C. albicans</td>
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<td>100</td>
<td>0</td>
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<td>0.5</td>
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<tr>
<td>C. krusei</td>
<td>84</td>
<td></td>
<td>98.8</td>
<td>14.3</td>
<td>1.2</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>C. parapsilosis</td>
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<td></td>
<td>100</td>
<td>5.5</td>
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<td>0.5</td>
<td>1</td>
</tr>
<tr>
<td>C. dubliniensis</td>
<td>30</td>
<td></td>
<td>100</td>
<td>0</td>
<td>0</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>C. utilis***</td>
<td>30</td>
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<td>93.3</td>
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<td>0.5</td>
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<td>C. pelliculosa***</td>
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<td>96.4</td>
<td>3.6</td>
<td>0</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>C. tropicalis</td>
<td>25</td>
<td></td>
<td>100</td>
<td>0</td>
<td>0</td>
<td>0.5</td>
<td>1</td>
</tr>
<tr>
<td>C. kefyr</td>
<td>22</td>
<td></td>
<td>100</td>
<td>9.1</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>C. lusitaniae**</td>
<td>22</td>
<td></td>
<td>100</td>
<td>4.5</td>
<td>0</td>
<td>0.5</td>
<td>1</td>
</tr>
</tbody>
</table>

* MIC 1-2 mcg/ml within limits sensitive. Requires will be treated only with high dose amphotericin B. Emergency from the development of resistance.

** In vivo C. lusitaniae resistant on amphotericin B.

*** Pichia is very rare. This 2 Candida are the same family Pichia. Pichia yet about ten year most often isolated on the child hematogy.

M. Jandrić 2013.
Anidulafungin in the treatment of IFI
Division of Hematology, UHC Zagreb

• No of patients: 20
• Age (median, range) 58 (22-74. g)
• Sex: M : 6, F : 14.
Anidulafungin in the treatment of IFI (N=20):

- Autologous SCT: 3
  - (BEAC, BEAM, R-Thiotepa BUCY)
- Allogeneic SCT: 7
  - (FluBuATG)
- Chemotherapy: 10
  - (HAM, HyperCVAD, Hovon 71, R-CHOP, VAD, azacitidin, miniMICE, VAD)
Characteristics of patients - Risk factors:

- Fungal lung infiltrate in the previous neutropenic episode, 6
- Neutropenia: 16
- Immunosuppressive therapy: 8 (CSP, mycophenolate mofetil, metilprednisolone)
- Neutropenia and immunosuppression: 5
Prophylactic use (N=4):

• mucositis (1), intestinal GVHD (1) - unable to use peroral posaconazole
• liver toxicity of posaconazole (1)
• mechanical ventilation - heavy colonization – tracheal aspirate (1)
Therapeutic use of anidulafungin (N=16):

• Probable lung fungal infection : (7)
  – lung infiltrate - MSCT, BAL - C. glabrata (1),
  sputum (3) Candida spp., Candida albicans, Candida guiliermondi

• Fungal sepsis: (3)
  – blood culture Candida spp., Candida glabrata

• Perianal abscess: (1)
  – isolate – C. glabrata

• Esophageal candidiasis (1)
Previous antifungal prophylaxis/therapy:

- Posaconazole: 7
- Fluconazole: 6
- Voriconazole: 2
OUTCOME:

PROPHYLAXIS (N=4)

- Recovery – no fungal infections – 3
- Lung infection – 1
  Lung infiltrates successfully treated with posaconazole, levofloxacin and tigecycline

THERAPY (N=16)

- Resolution of signs of infection - (13)
- Progression – (2) one case of febrile neutropenia, susequently established dg. of L. monocytogenes meningitis; another patient responded to amfotericin B;
- Death – (1) refractory AML, fungal sepsis (Candida glabrata)
SUMMARY Anidulafungin

- Superior efficacy to fluconazole in adult non-neutropenic patients\(^1\), AI recommended\(^8,9\)
- Proven efficacy in complex patients, including neutropenic patients\(^2,3,4\)
- Good safety profile
- No known interactions
- May represent a cost-effective choice\(^6,7\)

- UHC Zagreb experience – relatively small number of patients but positive outcome – efficient, good safety profile

Conclusions

• Optimal treatment strategies need to be tailored according to:
  – Local fungal epidemiology
  – Patients’ risk categories
  – Available diagnostic possibilities
  – Available therapeutic options

• Institutions treating high-risk patients should:
  – Organize multidisciplinary teams
  – Implement and use all relevant diagnostic methods
  – Be rational in treatment decisions
Managing invasive fungal infections:

- knowledge
- experience
- and...

The essence of wisdom is the ability to make the right decision on the basis of inadequate evidence

Alan Gregg