Management of Invasive Fungal Infections in Patients with Haematological Malignancies

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Ankara, Turkey
Outline

● Epidemiological characteristics of invasive fungal infections
● Multidisciplinary collaboration
● Diagnose correctly at earliest possibility
● Optimize antifungal use in hospitalized patients
● Limit the unnecessary use of antifungals
Stratification of Risk for IFD

- **Transplant**
  - HSCT, auto vs allo; donor source; GVHD; CMV
- **Immune**
  - Neutropenia, lymphopenia, steroids, purine analogues, mAbs…
- **Co-morbidities**
  - Diabetes, lung pathology, smoking
- **Environment**
  - Weather, occupation, locality, building works…
- **Genetics**
  - IL-10, TNF-α, TLR, plasminogen, MBL…

CMV, cytomegalovirus; GVHD, graft vs host disease; HSCT, hematopoietic stem cell transplant
Annual Incidence Rates for Invasive Fungal Infections in Patients with Hematologic Malignancies


n=538 invasive fungal infections
Incidence of Invasive Fungal Infections in Hematological Malignancies

Retrospective study of invasive fungal infections in all patients with newly diagnosed hematologic malignancies in 18 hematology wards in Italy, 1999–2003

(n = 11,802 patients)

ALL, acute lymphoid leukemia; AML, acute myeloid leukemia; CLL, chronic lymphoid leukemia; CML, chronic myeloid leukemia; HD, Hodgkin's disease; MM, multiple myeloma; NHL, non-Hodgkins lymphoma

Mortality Rates of Invasive Fungal Infections

- All-cause mortality of IC compared with IA from 1991 to 2003

IA, invasive aspergillosis; IC, invasive candidiasis
Candidemia in Europe

Distribution of Candida species

<table>
<thead>
<tr>
<th>Category</th>
<th>Percent</th>
<th>Species</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery (933)</td>
<td>100</td>
<td>Other</td>
</tr>
<tr>
<td>Intensive care (839)</td>
<td>100</td>
<td>Other</td>
</tr>
<tr>
<td>Solid tumour (471)</td>
<td>100</td>
<td>Other</td>
</tr>
<tr>
<td>Haematologic malignancy (257)</td>
<td>100</td>
<td>Other</td>
</tr>
<tr>
<td>Foetal immaturity (124)</td>
<td>100</td>
<td>Other</td>
</tr>
<tr>
<td>HIV infection (63)</td>
<td>100</td>
<td>Other</td>
</tr>
</tbody>
</table>

Other, C. tropicalis, C. glabrata, C. parapsilosis, C. albicans

### EORTC-IDG Fungemia Cohort

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>145,030</td>
</tr>
<tr>
<td>Hospitals</td>
<td>13</td>
</tr>
<tr>
<td>Countries</td>
<td>8</td>
</tr>
<tr>
<td>Fungemia episodes</td>
<td>333 (2.3‰, 95% CI, 2.1-2.6)</td>
</tr>
<tr>
<td>Solid tumor</td>
<td>1.5‰</td>
</tr>
<tr>
<td>HSCT</td>
<td>14.6‰</td>
</tr>
<tr>
<td><strong>Isolates</strong></td>
<td></td>
</tr>
<tr>
<td>Candida</td>
<td>267 (90%)</td>
</tr>
<tr>
<td><em>C. albicans</em></td>
<td>128 (48%)</td>
</tr>
<tr>
<td>non-albicans Candida</td>
<td>145 (54%)</td>
</tr>
<tr>
<td>non-Candida</td>
<td>31 (10%)</td>
</tr>
</tbody>
</table>

EORTC-IDG, European Organisation for Research and Treatment of Cancer Infectious Diseases Group; HSCT, hematopoietic stem cell transplant
Candidemia in Prospective Antifungal Therapy (PATH) Alliance Trial

- 2019 patients
  - 1 July 2004–5 March 2008
- *C. albicans* (45.6%)
- Crude mortality, 12 week 35.2%
  - *C. parapsilosis* 23.7%
  - *C. krusei* 52.9%

Distribution of *Candida* Species PATH Registry

<table>
<thead>
<tr>
<th>Species</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>albicans</td>
<td>921</td>
</tr>
<tr>
<td>glabrata</td>
<td>525</td>
</tr>
<tr>
<td>paraps.</td>
<td>316</td>
</tr>
<tr>
<td>tropicalis</td>
<td>163</td>
</tr>
<tr>
<td>krusei</td>
<td>51</td>
</tr>
<tr>
<td>lusitan.</td>
<td>17</td>
</tr>
<tr>
<td>others</td>
<td>26</td>
</tr>
</tbody>
</table>
Survival at 12 Weeks – PATH

PATH, Prospective Antifungal Therapy
Candidemia in Hacettepe

- 2001-2010, retrospective analysis
- 18,426 positive blood cultures
  - 858 Candida-positive blood cultures
  - 381 isolates, single patient, first episode
    - Candida ranked as the 5th most frequent isolate

Hacettepe Candidemia Isolates

n=381

C. albicans  C.parapsilosis  C.tropicalis  C.glabrata  Others

Candidemia-Underlying Diseases
Hacettepe 2001–2010

ICU, intensive care unit
Candida spp. Underlying Diseases
Hacettepe 2001–2010

NAC, non-albicans species
Hacettepe Candidaemia Isolates 2011–2016, N=328

<table>
<thead>
<tr>
<th>Year</th>
<th>Candida albicans</th>
<th>Non-albicans Candida</th>
</tr>
</thead>
<tbody>
<tr>
<td>2011</td>
<td>20</td>
<td>15</td>
</tr>
<tr>
<td>2012</td>
<td>25</td>
<td>20</td>
</tr>
<tr>
<td>2013</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>2014</td>
<td>35</td>
<td>35</td>
</tr>
<tr>
<td>2015</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>2016</td>
<td>25</td>
<td>25</td>
</tr>
</tbody>
</table>

Candida auris

- MDR yeast associated with high mortality
- First reported in 2009 from external ear discharge, Japan
- C. auris identified: India, Colombia, Venezuela, Pakistan, UK, US, others
- Most infections: hospital-associated, often several weeks after admission
- Bloodstream and other infections

Hematological Malignancy and Fungal Infection

TRANSNET study\(^1\)
- 425 cases of invasive aspergillosis observed in 875 HSCT recipients
- Median time to onset: 99 days
- Consistent with other data – median time to diagnosis after HSCT was 82 days\(^2\)
- Most (84\%) cases occurred within first year…
- …however, 16\% of cases occurred after 1 year


HSCT, hematopoietic stem cell transplant
Incidence of IFI in HSCT
Conventional vs Postmortem Diagnosis

Aspergillosis was the most common IFI reported in these studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Mortality (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ullman (2007)</td>
<td>3.0</td>
</tr>
<tr>
<td>Wingard (2010)</td>
<td>10.5</td>
</tr>
<tr>
<td>TRANSNET (2010)</td>
<td>8.1</td>
</tr>
<tr>
<td>Chamilos (2006)</td>
<td>30.3</td>
</tr>
</tbody>
</table>

HSCT, hematopoietic stem cell transplant; IFI, invasive fungal infection
Mortality Associated With Invasive Aspergillosis Decreasing Over Time

Reduction in mortality is likely due to the introduction of new generation antifungals

Median time to death due to invasive aspergillosis: 22 days (range: 3-58 days)³

Short- vs Long-Term Mortality in Patients with Invasive Aspergillosis

Long-term mortality is still high!

A multidisciplinary team approach to the management of patients with suspected or diagnosed invasive fungal disease

Ronen Ben-Ami1*, Kazimierz Halaburda2, Galina Klyasova3, Gökhan Metan4, Tigran Torosian5 and Murat Akova6

1Infectious Diseases Unit, Tel Aviv Sourasky Medical Center and Sackler School of Medicine, Tel Aviv University, Israel; 2Department of Stem Cell Transplantation, Institute of Haematology and Transfusion Medicine, Warsaw, Poland; 3Department of Clinical Microbiology, Mycology and Antibiotic Therapy, Russian Haematological Centre, Moscow, Russia; 4Department of Infectious Diseases and Clinical Microbiology, Faculty of Medicine, Erzurum University, Kayseri, Turkey; 5Department of Haematology, Oncology and Internal Medicine, Medical University of Warsaw, Poland; 6Department of Infectious Diseases, Hacettepe University School of Medicine, Ankara, Turkey

*Corresponding author. Tel: +972-3-6974347; Fax: +972-3-6974996; E-mail: ronenbo@tlvmc.gov.il
Figure 1. Diagram of the key members of the IFD-MDT.

IFD, invasive fungal disease; MDT, multidisciplinary team
Difficulties in the Management of Invasive Fungal Infections

- Inability to avoid predisposing factors
- Lack of diagnostic facilities
- Limited therapeutic options
  - Toxicity, interactions, cost, clinical resistance
- Biased clinical trials
- Impossibility to control IFI without correction of the predisposing factors
Early Diagnosis of Invasive Fungal Infections

● Obstacles
  – Signs and symptoms may be absent because of immune defect or immunosuppression
  – Few organism-specific clinical features
  – Fungi are colonizers as well as pathogens
  – Limited early diagnostic tools
  – Tissue diagnosis often necessary but difficult to obtain

● Benefit
  – Early and appropriate intervention decreases mortality
Tools for the Diagnosis of Invasive Aspergillosis

- High-resolution chest CT
  - Identification of a suspicious/unexplained pulmonary lesion

- Galactomannan assay, β-D-glucan assay, PCR
  - Marker positivity in serum or BAL fluid

de Pauw BE, Donnelly JP. Clin Infect Dis. 2009;48:1052
Chest CT Scan Findings in Neutropenic Patients with Invasive Aspergillosis

Retrospective analysis of chest CT scans of 235 patients with proven or probable IPA

- air bronchograms (16%), cluster of small nodules <1 cm in diameter (11%), pleural effusion (11%), and air crescent

* air bronchograms (16%), cluster of small nodules <1 cm in diameter (11%), pleural effusion (11%), and air crescent

Diagnosis: CT Scan

Halo sign
- D0: 96%
- D3: 68%
- D7: 22%
- D14: 19%

Non-specific consolidation
- D0
- D3: 31%
- D7: 50%
- D14: 18%

Air crescent sign
- D0: 0%
- D3: 8%
- D7: 28%
- D14: 63%

Patients Treated for Invasive Aspergillosis Based on Finding of Halo Sign Had Improved Outcomes

Halo sign

Probability of Survival

Hazard ratio: 0.571
Log rank P < 0.01

Chest CT Findings May Differ Depending on Stage of Disease

- Histopathology findings
  - AL/allo HSCT (preengraftment): minimal inflammation, hyphal invasion with high fungal burden, extensive necrosis
  - Classical signs common
  - Allo HSCT (post-engraftment): severe lung inflammation and low fungal burden
  - Classical signs less common

Incidence (%)

<table>
<thead>
<tr>
<th></th>
<th>Angioinvasive (macronodule, halo sign)</th>
<th>Airway-invasive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute Leukemia</td>
<td>45</td>
<td>13</td>
</tr>
<tr>
<td>Allogeneic HSCT</td>
<td>14</td>
<td>44</td>
</tr>
</tbody>
</table>

Galactomannan and Beta Glucan in Proven / Probable Invasive Aspergillosis

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta Glucan</td>
<td>88</td>
<td>90</td>
<td>70</td>
<td>96</td>
</tr>
<tr>
<td>Galactomannan</td>
<td>88</td>
<td>90</td>
<td>70</td>
<td>96</td>
</tr>
<tr>
<td>Combined analysis*</td>
<td>88</td>
<td>100</td>
<td>100</td>
<td>96</td>
</tr>
</tbody>
</table>

*Early positivity with beta-glucan

Serial Galactomannan Testing in BAL

- BAL GM testing may be more useful with reduce fungal load and circulating GM levels
  - Mould-active antifungal prophylaxis
  - Corticosteroid-induced immunosuppression

<table>
<thead>
<tr>
<th>Cutoff</th>
<th>Studies, n</th>
<th>Pooled Sensitivity</th>
<th>Pooled Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>24</td>
<td>87%</td>
<td>89%</td>
</tr>
<tr>
<td>1.0</td>
<td>21</td>
<td>86%</td>
<td>95%</td>
</tr>
<tr>
<td>1.5</td>
<td>10</td>
<td>85%</td>
<td>95%</td>
</tr>
<tr>
<td>2.0</td>
<td>8</td>
<td>84%</td>
<td>95%</td>
</tr>
<tr>
<td>2.5</td>
<td>6</td>
<td>80%</td>
<td>95%</td>
</tr>
</tbody>
</table>

Outcomes After Galactomannan-Based Diagnosis of IA

Basis for Diagnosis of Aspergillosis

- Galactomannan: 79%
- BAL culture or cytology: 18%
- Tissue culture and/or histopathology: 3%

Data on file. Pfizer, Inc.

All-Cause Mortality at 6 Weeks

- Tissue/Histopathology: 44.4%
- BAL Culture or Cytology: 28.0%
- Galactomannan: 21.6%
β-D-Glucan in Invasive Aspergillosis

- β-D-glucan is a cell wall component of most fungi
  - Exceptions: Zygomycetes, Cryptococcus

- Diagnostic accuracy in patients with proven/probable IFI
  - Sensitivity: 76.8%
  - Specificity: 85.3%

- Not universally used, and of limited use for detection of IA in immunocompromised patients

<table>
<thead>
<tr>
<th>Study</th>
<th>Cutoff (pg/mL)</th>
<th>Systemic Candida %</th>
<th>IA, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hachem 2009</td>
<td>80*</td>
<td>62</td>
<td>67</td>
</tr>
<tr>
<td>Roo 2009</td>
<td>80</td>
<td>63</td>
<td>75</td>
</tr>
<tr>
<td>Obayashi 2008</td>
<td>30</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Persat 2008</td>
<td>80</td>
<td>85</td>
<td>69</td>
</tr>
<tr>
<td>Senn 2008</td>
<td>7*</td>
<td>59</td>
<td>60</td>
</tr>
<tr>
<td>Akamatsu 2007</td>
<td>40</td>
<td>50</td>
<td>100</td>
</tr>
<tr>
<td>Ostrosky-Zeichner 2005</td>
<td>80</td>
<td>78</td>
<td>80</td>
</tr>
<tr>
<td>Odabasi 2004</td>
<td>80</td>
<td>82</td>
<td>100</td>
</tr>
<tr>
<td>Mori 1997</td>
<td>1000</td>
<td>92</td>
<td>100</td>
</tr>
<tr>
<td>Mitsutake 1996</td>
<td>60</td>
<td>84</td>
<td>100</td>
</tr>
<tr>
<td>Miyazaki 1995</td>
<td>10</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td><strong>Total from all studies</strong></td>
<td><strong>75</strong></td>
<td><strong>77</strong></td>
<td></td>
</tr>
</tbody>
</table>

*Two consecutive values.

PCR Assays for *Aspergillus* Detection

- Allows for assay also in the presence of low levels of DNA in clinical samples
- Issues with standardization
- Currently best used in combination with other diagnostic tests

<table>
<thead>
<tr>
<th>PCR Assay</th>
<th>One Positive Result</th>
<th>Two Positive Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>88%</td>
<td>75%</td>
</tr>
<tr>
<td>Specificity</td>
<td>75%</td>
<td>87%</td>
</tr>
</tbody>
</table>

Fredricks DN, Relman DA. Clin Infect Dis. 1999;29:475
Factors for Selection of Antifungal Treatment

- Antifungal activity against a broad range of fungi
- Good PK properties
- Availability: IV and PO
- Ease of administration
- Low frequency of adverse events
- Minimal (ideally no) drug interactions
- Health economic impact

PK, pharmacokinetic
Polyenes

- Spectrum of activity similar deoxycholate vs lipid formulations (LFs)
  - Only toxicity differs
    - d-AmpB nephrotoxicity leads to 6.6-fold increase in mortality
  - No superiority for Candida
  - Different pharmacological properties
    - Reduced urinary concentrations for LFs
    - L-AmpB better penetrates into the CSF

**Triazoles**

- Fluconazole
- Itraconazole
- Voriconazole
- Posaconazole
- Isovuconazole

Each has similar activity to most Candida spp.
  - Less active against *C. glabrata* and *C. krusei*
Triazoles

- All inhibits cytochrome P450
- Fluconazole
  - Oral bioavailability 90%
  - Best penetration into the CSF, vitreus (>70% of serum)
  - X10-20 concentrates in urine

Other Triazoles

- **Itraconazole**
  - Not well studied in invasive candidiasis

- **Voriconazole**
  - CSF and vitreus concentrations >50% of serum
  - Not useful urine concentrations

- **Posaconazole and isovuconazole**
  - No primary candidiasis indication
  - Active against mucormycosis
Echinocandins

- Caspofungin
- Micafungin
- Anidulafungin
Echinocandins

- Low MICs for most Candida spp.
  - Tx failures with *C. glabrata*
  - Higher MICs for *C. parapsilosis*
  - Survival advantage of upfront therapy in non-neutropenic candidiasis
- No therapeutic levels in eye, CNS and urine
- No dosage adjustment for renal failure
Flucytosine

- Broad activity against Candida spp. except *C. krusei*
- Good penetration in eye, CNS, urine
- Rapid development of resistance in monotherapy
- 80-90% oral bioavailability
## Treatment Strategies Defined

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prophylaxis</strong></td>
<td>All patients at high risk of IFD</td>
</tr>
<tr>
<td><strong>Empirical therapy</strong></td>
<td>Persistent neutropenic fever (4–7 days)</td>
</tr>
<tr>
<td></td>
<td>Despite broad spectrum antibiotics</td>
</tr>
<tr>
<td></td>
<td>Microbiology negative</td>
</tr>
<tr>
<td><strong>Pre-emptive</strong> (Diagnostic driven) therapy</td>
<td>Persistent neutropenic fever (4–7 days)</td>
</tr>
<tr>
<td></td>
<td>Laboratory* or radiologic** markers indicating IFD</td>
</tr>
<tr>
<td><strong>Documented therapy</strong></td>
<td>EORTC/MSG criteria for probable or proven IFD</td>
</tr>
</tbody>
</table>

*Positive Aspergillus galactomannan, PCR or β-D-Glucan tests  
**E.g. halo sign on computed tomography (CT) scan

IFD, invasive fungal disease  
## Treatment of Candidemia in Neutropenics

<table>
<thead>
<tr>
<th>Therapy</th>
<th>ESCMID 2012</th>
<th>IDSA 2016</th>
</tr>
</thead>
<tbody>
<tr>
<td>Echinocandin</td>
<td>Caspo and Mica <strong>AII</strong>, Anidulam <strong>BII</strong></td>
<td>1st choice</td>
</tr>
<tr>
<td>Lipid AmpB</td>
<td>L AmpB <strong>BII</strong>, ABLC <strong>CII</strong></td>
<td>Effective, but less attractive due to toxicity</td>
</tr>
<tr>
<td>Fluconazole</td>
<td><strong>CII</strong>, step down tx</td>
<td>Step down therapy, not seriously ill and no previous exposure to flu</td>
</tr>
<tr>
<td>Voriconazole</td>
<td><strong>CII</strong>, limited data, better then fluconazole</td>
<td>Additional mold coverage, step down tx</td>
</tr>
<tr>
<td>CVC removal</td>
<td>Less clear than non-neutropenics, survival advantage</td>
<td>Decision on individual basis</td>
</tr>
</tbody>
</table>

### Practice Guidelines for the Diagnosis and Management of Aspergillosis: 2016 Update by the Infectious Diseases Society of America

<table>
<thead>
<tr>
<th>Condition</th>
<th>Primary therapy</th>
<th>Alternative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Invasive Pulmonary</td>
<td>Voriconazole</td>
<td>L-AMB, isavuconazole, echinocandin, posaconazole, itraconazole</td>
</tr>
<tr>
<td>Invasive sinus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tracheobronchial</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CNS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone/joint</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart (endocarditis, etc)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eye</td>
<td>Intraocular AMB</td>
<td>AND voriconazole</td>
</tr>
<tr>
<td>Empiric or Pre-emptive</td>
<td>L-AMB, itraconazole, voriconazole</td>
<td></td>
</tr>
<tr>
<td>Prophylaxis</td>
<td>Posaconazole</td>
<td>Itraconazole, micafungin</td>
</tr>
<tr>
<td>Chronic necrotizing</td>
<td>Itraconazole, voriconazole</td>
<td></td>
</tr>
<tr>
<td>Allergic bronchopulmonary aspergillosis (ABPA)</td>
<td>Itraconazole</td>
<td>voriconazole, posaconazole</td>
</tr>
</tbody>
</table>

ECIL-6 Guidelines For The Treatment Of Invasive Candidiasis, Aspergillosis And Mucormycosis In Leukemia And Hematopoietic Stem Cell Transplant Patients

Frederic Tissot, Samir Agrawal, Livio Pagano, Georgios Petrikkos, Andreas H. Groll, Anna Skiada, Cornelia Lass-Flörl, Thierry Calandra, Claudio Viscoli, Raoul Herbrecht

<table>
<thead>
<tr>
<th>Antifungal agent</th>
<th>Grade</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Voriconazole</td>
<td>A I</td>
<td>Daily dose: 2x6 mg/kg on day 1 then 2x4 mg/kg (initiation with oral therapy; C III)</td>
</tr>
<tr>
<td>Isavuconazole</td>
<td>A I</td>
<td>As effective as voriconazole and better tolerated</td>
</tr>
<tr>
<td>Liposomal amphotericin B</td>
<td>B I</td>
<td>Daily dose: 3 mg/kg</td>
</tr>
<tr>
<td>Amphotericin B lipid complex</td>
<td>B II</td>
<td>Daily dose: 5 mg/kg</td>
</tr>
<tr>
<td>Amphotericin B colloidal dispersion</td>
<td>C I</td>
<td>Not more effective than d-AmB but less nephrotoxic</td>
</tr>
<tr>
<td>Caspofungin</td>
<td>C II</td>
<td></td>
</tr>
<tr>
<td>Itraconazole</td>
<td>C III</td>
<td></td>
</tr>
<tr>
<td>Combination voriconazole* + anidulafungin</td>
<td>C I</td>
<td></td>
</tr>
<tr>
<td>Other combinations</td>
<td>C III</td>
<td></td>
</tr>
<tr>
<td>Recommendations against d-AmB use</td>
<td>A I</td>
<td></td>
</tr>
</tbody>
</table>

NB: In the absence of sufficient data for first-line monotherapy, anidulafungin, micafungin and posaconazole have not been graded.

Empirical Antifungal Therapy

Empirical
- No diagnostic facilities available
- Use only to buy time

Refactory fever
(3–7 days)

Clinical features

Treatment

Diagnosis

Continue/change treatment

IMD

IMD not confirmed

Response at day 7

Review treatment*

No

Yes

Duration of therapy
‘Step down’
Out-patient follow up

Diagnostic Driven Antifungal Therapy


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Which Strategy to Choose?

- **Immunosuppressed**
  - Incidence
  - Availability of Dx tests

- **Non-Immunosuppressed**
  - Prophylaxis
  - Empirical
  - Pre-Emptive
  - Targeted
Conclusions

- Invasive fungal infections are significant cause of morbidity and mortality in haematological cancer patients
- Early diagnosis are challenging
- Treatment strategies should be adapted according to the local diagnostic facilities
Thank you...