Fungal Infections in Immunocompromised Host

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Ankara, Turkey
Epidemiology of Sepsis in the US 1979-2000

# Candida as a Nosocomial Pathogen

<table>
<thead>
<tr>
<th>Rank</th>
<th>Pathogen</th>
<th>BSI per 10,000 admissions</th>
<th>Total (n=20,978)</th>
<th>ICU (n=10,515)</th>
<th>Non-ICU (n=10,515)</th>
<th>Total</th>
<th>ICU</th>
<th>Non-ICU</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>CoNS</td>
<td>15.8</td>
<td>31.3</td>
<td>35.9</td>
<td>26.6</td>
<td>20.7</td>
<td>25.7</td>
<td>13.8</td>
</tr>
<tr>
<td>2.</td>
<td>S aureus</td>
<td>10.3</td>
<td>20.7</td>
<td>16.8</td>
<td>23.7</td>
<td>25.4</td>
<td>34.4</td>
<td>18.9</td>
</tr>
<tr>
<td>3.</td>
<td>Enterococcus spp</td>
<td>4.8</td>
<td>9.4</td>
<td>9.8</td>
<td>9.0</td>
<td>33.9</td>
<td>43.0</td>
<td>24.0</td>
</tr>
<tr>
<td>4.</td>
<td>Candida spp</td>
<td>4.6</td>
<td>9.0</td>
<td>10.1</td>
<td>7.9</td>
<td>39.2</td>
<td>47.1</td>
<td>29.0</td>
</tr>
<tr>
<td>5.</td>
<td>E coli</td>
<td>2.8</td>
<td>5.6</td>
<td>3.7</td>
<td>7.6</td>
<td>22.4</td>
<td>33.9</td>
<td>16.9</td>
</tr>
<tr>
<td>6.</td>
<td>Klebsiella spp</td>
<td>2.4</td>
<td>4.8</td>
<td>4.0</td>
<td>5.5</td>
<td>27.6</td>
<td>37.4</td>
<td>20.3</td>
</tr>
<tr>
<td>7.</td>
<td>P aeruginosa</td>
<td>2.1</td>
<td>4.3</td>
<td>4.7</td>
<td>3.8</td>
<td>38.7</td>
<td>47.9</td>
<td>27.6</td>
</tr>
<tr>
<td>8.</td>
<td>Enterobacter spp</td>
<td>1.9</td>
<td>3.9</td>
<td>4.7</td>
<td>3.1</td>
<td>26.7</td>
<td>32.5</td>
<td>18.0</td>
</tr>
<tr>
<td>9.</td>
<td>Serratia spp</td>
<td>0.9</td>
<td>1.7</td>
<td>2.1</td>
<td>1.3</td>
<td>27.4</td>
<td>33.9</td>
<td>17.1</td>
</tr>
<tr>
<td>10.</td>
<td>A baumannii</td>
<td>0.6</td>
<td>1.3</td>
<td>1.6</td>
<td>0.9</td>
<td>34.0</td>
<td>43.4</td>
<td>16.3</td>
</tr>
</tbody>
</table>

Candidaemia: the European Experience

Review

Candidaemia in Europe: epidemiology and resistance

Anna Maria Tortorano\textsuperscript{a, x}, Christopher Kibbler\textsuperscript{b}, Javier Peman\textsuperscript{c}, Hannelore Bernhardt\textsuperscript{d}, Lena Klingspor\textsuperscript{e}, Renee Grillot\textsuperscript{f}

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\textsuperscript{b} Department of Medical Microbiology, Royal Free Hospital, Pond Street, London NW3 2QG, UK
\textsuperscript{c} Servicio de Microbiología, Hospital La Fe, Avda Campanar 21, 46009 Valencia, Spain
\textsuperscript{d} Clinic of Internal Medicine A and Loeffler Institute of Medical Microbiology, Ernst Moritz Arndt Universität Greifswald, Friedrich Loeffler Str. 23a, 17487 Greifswald, Germany
\textsuperscript{e} Department of Clinical Bacteriology, Karolinska Institute, Huddinge University Hospital, 14186 Huddinge, Sweden
\textsuperscript{f} Service de Parasitologie–Mycologie, Centre Hospitalier Universitaire, BP 217, 38043 Grenoble Cedex 9, France
## Table 2
Underlying pathology/medical care of patients with candidaemia ($n = 2089$; more than one may be present in each episode)

<table>
<thead>
<tr>
<th>Condition</th>
<th>No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery</td>
<td>1007</td>
<td>48.2</td>
</tr>
<tr>
<td>Intensive care</td>
<td>839</td>
<td>40.2</td>
</tr>
<tr>
<td>Solid tumour</td>
<td>471</td>
<td>22.5</td>
</tr>
<tr>
<td>Steroids</td>
<td>364</td>
<td>17.4</td>
</tr>
<tr>
<td>Haematological malignancy</td>
<td>257</td>
<td>12.3</td>
</tr>
<tr>
<td>Premature birth</td>
<td>125</td>
<td>6.0</td>
</tr>
<tr>
<td>HIV infection</td>
<td>63</td>
<td>3.0</td>
</tr>
<tr>
<td>Burns</td>
<td>29</td>
<td>1.4</td>
</tr>
</tbody>
</table>
Candidaemia in Europe

Distribution of Candida species

Tortorano et al., Int J Antimicrob Agents 2006; 27: 359
“Candida Score” in Critically Ill Patients

- 73 medical-surgical ICU in Spain
- 1699 patients, ≥7 d stay in ICU
  - Multifocal colonization (+1.112)
  - Parenteral nutrition (+0.908)
  - Surgery (+0.997)
  - Severe sepsis (+2.038)
- A score >2.5 accurately selects for early antifungal therapy

Treatment of Candidiasis

• **Candidemia in non-neutropenic patients**
  – Fluconazole or echinocandin
  – Alternatives: L-AmpB or voriconazole

• **Candidemia in neutropenic patients**
  – Echinocandin or L-AmpB
  – Alternatives: Fluconazole or voriconazole

• **Empirical tx for suspected candidemia**
  – **Non-neutropenics**: Same agents
  – **Neutropenics**: L-AmpB, caspofungin, voriconazole
    - Alternatives: Fluconazole or itraconazole

Mortality due to Candidemia and Time for Initiating Fluconazole Therapy

Day when fluconazole tx initiated

Delaying the Empirical Treatment of Candidemia

Hospital mortality

n=157 patients with candidemia

Hours when antifungal therapy applied after blood cultures taken

<12 12-24 24-48 >48

Invasive Aspergillosis Mortality

Between 1995-99
50 studies,
1941 patients

Survival and Prognostic Factors for Invasive Aspergillosis in HSCT

- Non-myeloablative conditioning
- Peripheral blood stem cells
- Earlier diagnosis
- Use of voriconazole

Invasive Aspergillosis in Patients with Acute Leukemia


Improved Treatment

↑probable IA GM-PCR-CT

P = .002

(incidence)

Outcome in Invasive Aspergillosis by Karnofsky Score

<table>
<thead>
<tr>
<th></th>
<th>&lt; 50</th>
<th>50-60</th>
<th>&gt; 60</th>
</tr>
</thead>
<tbody>
<tr>
<td>Success EOT</td>
<td>40</td>
<td>30</td>
<td>20</td>
</tr>
<tr>
<td>P-value</td>
<td>0.04</td>
<td>0.009</td>
<td>0.009</td>
</tr>
<tr>
<td>Stabilization EOT</td>
<td>30</td>
<td>20</td>
<td>10</td>
</tr>
<tr>
<td>Survival Wk 12</td>
<td>10</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

EORTC 65041
Outcome in Invasive Aspergillosis by Neutrophil Recovery

- Success EOT: P=0.08
- Stabilization EOT: P=0.03
- Survival Wk 12: P<0.001

EORTC 65041
Clinical and Radiological Predictors of IA in Cancer Patients

Hachem R et al. Cancer 2006; 106: 1581
Clinical and Radiological Predictors of IA in Cancer Patients

Odds ratio for risk of IPA Multiple Regression Model

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukemia</td>
<td>3.00</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>4.30</td>
</tr>
<tr>
<td>Cavitary lesions</td>
<td>10.96</td>
</tr>
<tr>
<td>Nodular lesions</td>
<td>4.83</td>
</tr>
</tbody>
</table>

# Sensitivity of Conventional Diagnostic Procedures

<table>
<thead>
<tr>
<th>Site of infection</th>
<th>Procedure</th>
<th>% performed</th>
<th>% sensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pulmonary</strong></td>
<td>Chest X-ray</td>
<td>98</td>
<td>77</td>
</tr>
<tr>
<td></td>
<td>BAL culture</td>
<td>38</td>
<td>62</td>
</tr>
<tr>
<td></td>
<td>Sputum</td>
<td>72</td>
<td>58</td>
</tr>
<tr>
<td></td>
<td>Nasal swab</td>
<td>56</td>
<td>32</td>
</tr>
<tr>
<td></td>
<td>Surgical specimen</td>
<td>18</td>
<td>87</td>
</tr>
<tr>
<td><strong>Cerebral</strong></td>
<td>Cerebral CT</td>
<td>65</td>
<td>88</td>
</tr>
<tr>
<td></td>
<td>Surgical specimen</td>
<td>8</td>
<td>66</td>
</tr>
<tr>
<td><strong>Sino-nasal</strong></td>
<td>Cranial CT</td>
<td>50</td>
<td>86</td>
</tr>
<tr>
<td></td>
<td>Nasal swab</td>
<td>71</td>
<td>85</td>
</tr>
<tr>
<td></td>
<td>Surgical specimen</td>
<td>19</td>
<td>100</td>
</tr>
</tbody>
</table>

Pagano et al. Haematologica 2001; 86: 862
Diagnosis: CT SCAN

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

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

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

Aspergillosis in the ICU – The new 21st century problem?

KOENRAAD H. VANDERWOUDE*, DIRK VOGELAERS† & STIJN L. BLOT*

*Department of Intensive Care, Ghent University Hospital, Ghent, Belgium, and †Department of Internal Medicine – Center for Infectious Diseases, Ghent University Hospital, Ghent, Belgium

Outdoor air

Indoor air

Food items: Tea!

The home environment
## Aspergillosis in the ICU - The new 21st century problem?

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Type of study</th>
<th>Patient category</th>
<th>No. with invasive disease</th>
<th>Incidence</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lewis [9]</td>
<td>1985</td>
<td>Case series</td>
<td>IPA complicating influenza pneumonia Case report and literature review</td>
<td>6</td>
<td>6</td>
<td>100%</td>
</tr>
<tr>
<td>Karam [10]</td>
<td>1986</td>
<td>Cases series</td>
<td>Non-neutropenic patients 10 structural lung disease 7 steroid treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Janssen [36]</td>
<td>1996</td>
<td>Monocentric Retrospective</td>
<td>Medical ICU pts with hematological malignancy, immunosupression for mixed connective tissue disease, ARDS</td>
<td>25</td>
<td>25</td>
<td>92%</td>
</tr>
<tr>
<td>Pittet [11]</td>
<td>1996</td>
<td>Monocentric</td>
<td>COPD patients in MICU Acquisition of IPA during mechanical ventilation due to high grade airborne inoculation</td>
<td>2</td>
<td>2</td>
<td>100%</td>
</tr>
<tr>
<td>Rello [12]</td>
<td>1998</td>
<td>Monocentric</td>
<td>Series of COPD patients and literature review</td>
<td>24</td>
<td>24</td>
<td>100%</td>
</tr>
<tr>
<td>Valles [13]</td>
<td>2002</td>
<td>Two centres observational, prospective study</td>
<td>Hospital acquired pneumonia requiring ICU admission <em>Aspergillus</em> spp. identified in 17% of pts</td>
<td></td>
<td></td>
<td>77%</td>
</tr>
<tr>
<td>Bulpa [14]</td>
<td>2001</td>
<td>Monocentric Case series</td>
<td>COPD patients admitted to ICU diagnosed with IPA</td>
<td>23</td>
<td>23</td>
<td>100%</td>
</tr>
<tr>
<td>Meersseman [3]</td>
<td>2004</td>
<td>Monocentric Retrospective</td>
<td>Medical ICU 70% cases without malignancy 5 pts with 1A without known predisposing condition (of whom 3 Child C cirrhosis)</td>
<td>107</td>
<td>107</td>
<td>91%</td>
</tr>
<tr>
<td>Garnacho-Montero [4]</td>
<td>2005</td>
<td>Multicentric Prospective</td>
<td>73 ICUs in Spain patients with LOS &gt; 7 days</td>
<td>20</td>
<td>20</td>
<td>80%</td>
</tr>
<tr>
<td>Vandewoude [15]</td>
<td>2006</td>
<td>Retrospective</td>
<td>Mixed ICU 40% haematological pts</td>
<td>83</td>
<td>83</td>
<td>77%</td>
</tr>
</tbody>
</table>

Vandewoude et al. *Medical Mycology* 2006; 44: S71
• 9 month survey period / 73 ICUs
• 1756 patients
• Respiratory tract cultures
• *Aspergillus* species: recovered from 36 patients (2%)
  ✷ 14 patients: colonisation (11 left untreated, 50% mortality)
  ✷ 20 patients: invasive aspergillosis
  ✷ 2 patients: not classified
• Liposomal amphotericin B given to 8 patients with IA
  • clinical cure: 6/8 (75%)
Strategies for Treating IFI

- **Colonization**: "Marker-based strategy"?
- **Prophylaxis**: Targeted prophylaxis in high-risk patient.
- **Empirical**: High-risk patient on antibiotics with fever.
- **Therapy**: Full-blown disease.
- **Sequelae**: No disease.

Adapted from J. Maertens
Treatment Strategies to Overcome Mould Infections

- Accurate and rapid diagnosis
- Immune modulation: G or GM CSF; γ interferon
- Maximize antifungal dose (lipid AmB better and azole drug levels)
- Prophylaxis/empirical strategies
- Surgery (Zygomycetes and Aspergillus)
- Combination therapy
- New drugs
- Control of the underlying disease
### Aspergillosis Guidelines
**IDSA 2008**

<table>
<thead>
<tr>
<th></th>
<th><strong>IDSA</strong></th>
<th><strong>ECIL</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary tx</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Voriconazole</td>
<td>A-I</td>
<td>A-I</td>
</tr>
<tr>
<td>Ambisome®</td>
<td>A-I</td>
<td>B-I</td>
</tr>
<tr>
<td><strong>Salvage tx</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lipid Amp B</td>
<td>A-II</td>
<td>B-III</td>
</tr>
<tr>
<td>Posaconazole</td>
<td>B-II</td>
<td>B-II</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>B-II</td>
<td>C-III</td>
</tr>
<tr>
<td>Caspofungin</td>
<td>B-II</td>
<td>B-II</td>
</tr>
<tr>
<td>Micafungin</td>
<td>B-II</td>
<td>-</td>
</tr>
</tbody>
</table>

Unresponsive Cases

• Not enough data for vori unresponsive cases
  – Lipid Amp B or caspofungin (B-II)
  – Combination therapy (B-II)
    • Should not be employed routinely, needs further data
  – Therapeutic serum level monitoring may be required

Detection of multi-azole resistant *Aspergillus* in Dutch medical centers since 2002:

- Cross resistance to voriconazole, itraconazole, posaconazole, ravuconazole
- MICs 0.5-16 μg/ml
- A new *cyp51A* gene mutation in 12 of 13 isolates; not clonal
- Associated with itraconazole prophylaxis in 4
- Responses in most patients with voriconazole or posaconazole

Duration of Therapy

• Not clearly established
• 6-12 weeks generally recommended for immunocompromised patients
  – Until radiological clearance
  – Patients previously treated with antifungals should be given tx if they will become immunosuppressive again (A-III)

• Treatment follow up
  – CT and galactomannan levels (?)
    • Normalisation of galactomannan is not a criterium for stopping therapy (B-III)

‘PIRIS’

**Pulmonary Immune Reconstitution Inflammatory Syndrome**

- New onset / worsening clinical and radiological findings indicating an infectious/ inflammatory pulmonary condition
- Temporal relationship with neutrophil recovery
- Absence of new extrapulmonary lesions
- ≥ 50% decrease in serum GM titers without treatment modifications
- Subsequent resolution without treatment modification

Increased volume of lesion by CT not correlated with outcome

## Prognostic Factors for Attributable and Overall Mortality in IA in Cancer Patients

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Reference category</th>
<th>Hazard R*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allo-HSCT (or ST)</td>
<td>Hematological malignancy</td>
<td>1.78</td>
</tr>
<tr>
<td>Other host factors</td>
<td></td>
<td>1.52</td>
</tr>
<tr>
<td>Progression of underlying disease</td>
<td>No</td>
<td>4.54</td>
</tr>
<tr>
<td>Prior non-infectious respiratory disease</td>
<td>Absence</td>
<td>1.76</td>
</tr>
<tr>
<td>Steroid dose ( \geq 0.2 \text{ mg/kg} )</td>
<td>(&lt; 0.2 \text{ mg/kg} )</td>
<td>2.33</td>
</tr>
<tr>
<td>Creatinine clearance: 30-59 mL/min</td>
<td>( \geq 60 \text{ mL/min} )</td>
<td>1.65</td>
</tr>
<tr>
<td></td>
<td>(&lt; 30 \text{ mL/min} )</td>
<td>2.51</td>
</tr>
<tr>
<td>Monocytes &gt; 100/µL</td>
<td>( \leq 100/\mu\text{L} )</td>
<td>0.59</td>
</tr>
<tr>
<td>Site of infection</td>
<td>Disseminated</td>
<td>3.20</td>
</tr>
<tr>
<td></td>
<td>Lung only</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Other single organ</td>
<td>NA</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>Absence</td>
<td>1.77</td>
</tr>
<tr>
<td>Possible IA</td>
<td>Probable or definite</td>
<td>0.51</td>
</tr>
</tbody>
</table>

* All P-values are highly significant

Changing Spectrum of Invasive Molds

Incidence per 1000 Patient Days

Rate of aspergillosis

Aspergillus

Zygomycetes

Fusariosis 16%

Zygomycosis 20%

Invasive Aspergillosis 64%

Incidence of Zygomyces

n=929

Mortality Due to Mold Infections

11,802 patients (18 centers)

- Aspergillus spp: 42.0%
- Zygomycetes: 64.0%
- Fusarium spp: 52.0%

Range of Activity for Selected Pathogens

Candida albicans
Candida tropicalis
Candida parapsilosis
Candida krusei
Candida glabrata
Cryptococcus neoformans
Aspergillus fumigatus
Mucor spp
Rhizopus spp
Fusarium spp

Polyene; AMB = Amphotericin B
Azole; FCZ = Fluconazole; ITZ = Itraconazole; VZ = Voriconazole; PCZ = Posaconazole; RCZ = Ravuconazole
Echinocandin; CF = Caspofungin; MF = Micafungin; AF = Anidulafungin

Days from Symptoms to Initiation of Appropriate Therapy

Delaying Therapy and Mortality in Zygomycosis

Overall, n=70
≤6, n=35
>6, n=35

Days from symptoms to initiation of appropriate Tx.

% mortality at 12 weeks

65.7%
48.6% *
82.9%

*p=0.029, ≤6 days vs. >6 days

139 Zygomycosis Cases from 11 Countries (until August 2007)

- Austria: 10 cases
- Belgium: 4 cases
- Finland: 2 cases
- France: 15 cases
- Germany: 20 cases
- Greece: 26 cases
- Italy: 45 cases
- Norway: 2 cases
- Russia: 5 cases
- Spain: 9 cases
- UK: 1 case

Courtesy of George Petrikkos
Results: Underlying Diseases

- Hematologic malignancies: 46%
- Other malignancies: 4%
- Bone marrow transplantation: 7%
- Trauma: 17%
- Diabetes: 13%
- Solid organ transplantation: 4%
- Burn: 3%
- Other: 6%
- Other malignancies: 4%
- Hematologic malignancies: 46%

Courtesy of George Petrikkos
## Results: Prior use of drugs

<table>
<thead>
<tr>
<th></th>
<th>No</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Corticosteroids</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>64</td>
<td>46</td>
</tr>
<tr>
<td><strong>Immunosuppressants</strong></td>
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<td></td>
</tr>
<tr>
<td></td>
<td>49</td>
<td>35</td>
</tr>
<tr>
<td><strong>Antifungals</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Voriconazole</td>
<td>21</td>
<td>15</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>22</td>
<td>15</td>
</tr>
<tr>
<td>Liposomal amphotericin B</td>
<td>10</td>
<td>7</td>
</tr>
<tr>
<td>Caspofungin</td>
<td>18</td>
<td>12</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>4</td>
<td>2</td>
</tr>
</tbody>
</table>

*Courtesy of George Petrikkos*
Results: Site of infection

- Lung
- Rhinocerebral
- Sinus
- Bone
- Soft tissue
- Disseminated

Courtesy of George Petrikkos
Results: Underlying disease in relation to the site of infection

• Hematologic malignancy correlated with pulmonary disease
  – 30% patients with hematological malignancy had pulmonary zygomycosis
  – 56% patients with pulmonary zygomycosis had an underlying hematological malignancy

• Diabetes correlated with rhinocerebral disease
  – 59% patients with diabetes had rhinocerebral disease
  – 32% patients with rhinocerebral disease had diabetes

Courtesy of George Petrikkos
### Results: Treatment

<table>
<thead>
<tr>
<th>Treatment Type</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical</td>
<td>104</td>
<td>75</td>
</tr>
<tr>
<td>Surgical</td>
<td>55</td>
<td>40</td>
</tr>
<tr>
<td>Combination</td>
<td>51</td>
<td>37</td>
</tr>
<tr>
<td>None</td>
<td>10</td>
<td>7</td>
</tr>
</tbody>
</table>

**Medical treatment (n)**
- Liposomal amphotericin B (AmBisome®) \( n = 74 \)
- Deoxycholate amphotericin B \( n = 20 \)
- Lipid amphotericin B (Abelcet®) \( n = 4 \)
- Posaconazole \( n = 39 \)
- Caspofungin \( n = 11 \)
- Voriconazol \( n = 4 \)
- Itraconazole \( n = 3 \)
- Fluconazole \( n = 1 \)

*Courtesy of George Petrikkos*
Results: Mortality

- Patients who died 57 (50%)
- Data about outcome pending in 26 patients
- **Surgical treatment** related to decreased mortality (Odds ratio 0.28, 95% CI 0.11-0.74)
- Increased **age** was related to increased mortality (Odds ratio 1.04, 95% CI 1.01-1.07, p=0.005)
- Prior use of **voriconazole** was related to increased mortality (Odds ratio 9.1, 95% CI 1.8-53.3, p=0.009)
Conclusions

• Invasive fungal infections are a significant cause of morbidity and mortality in immunosuppressed patients.

• Despite availability of many new antifungals, better diagnostic and management strategies are yet to be developed.