Fungal infections in non-neutropenic surgical patients

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Risk factors
Candida infections
Therapy and prophylaxis
Conclusions
Fungal infection

To whom

Why

What

How much
No. of operations/year

- 330,000 operations
- 60,000 intraabdominal operations
- 4% at ICU = 2400 patients
- Non-neutropenic critically ill patients
Intra-abdominal infections

- Acute peritonitis
  - GI tract perforation
  - Necrosis of bowel/pancreas
  - Perviperitonitis
- Postoperative peritonitis
  - Leak of an anastomosis
  - Stump insufficiency
  - Other iatrogenic leaks
- Posttraumatic peritonitis
  - After blunt abdominal trauma
  - After penetrating trauma
- Tertiary peritonitis
- Intraabdominal abscess
- Severe pancreatitis
Re-operation

- Surgical trauma (decreased immune reaction)
- Blood transfusion (decreased immune reaction)

- Increased intraabdominal pressure (risk of renal failure)
- Use of loop-diuretics (risk of renal failure)
- Pressure support (risk of renal failure)
- Gentamicin has often been used (risk of renal failure)
- Increased level of toxins (risk of renal failure)
ICU

- Prolonged treatment with multiple broad-spectrum antibiotics
- Parenteral nutrition
- Renal and liver failure
- Mechanical ventilation
- Alteration of the endogenous flora

- Chemotherapy - drug, dose, and duration
- Radiotherapy
- Corticosteroids
- Malnutrition

G-I tract

• The G-I tract is a reservoir of Candida species and an important portal of intraabdominal infections.

• If Candida is not cleared from the peritoneal cavity, seeding results in the development of intra-abdominal Candida infection.

Immune reaction

Elective surgery
Reoperation

0  1  2  3  4  5  6  7  8  9  10          30   days
Change in balance between health and disease

- Fungal Infections
- Host Factors
- Environment
Fungi main players

• Yeast
  – Candida
  – Cryptococcus

• Mould
  – Aspergillus
  – Mucormycosis (zygomycosis)
Candida infections

- Candida affects high-risk patients who are either immunocompromised or critically ill

- About 25% to 50% of cases of nosocomial candidemia occur among patients in intensive care

- Lack of reliable diagnostic tools makes early detection of Candida infection difficult

- Candidiasis is associated with high rates of morbidity, mortality and results in high healthcare cost
Candida infections

- Candida is the fourth most common cause of bloodstream infections

- About 72% of all nosocomial fungal infections are caused by Candida species.

- During the past years there have been a shift in the predominant species responsible for invasive candidiasis in hospitalized patients, particularly to C. glabrata (20%), C. tropicalis (4%) and C. krusei (3%)

- Until recently few randomized trials

Aspergillus

Common cause of invasive fungal infection in neutropenic patients

- Species:  
  A. Fumingatus  
  A. Niger  
  A. Flavus  
  A. Glauces

- Organs most commonly involved:  
  - Lung  
  - Paranasal sinuses  
  - Brain  
  - GI tract  
  - Liver / spleen

Nosocomial fungal infection

1980 - 1990
7.3 per 1,000 patients following surgery

1991-1996
12.7 per 1,000 patients following surgery

1997 - 2005
16.1 per 1,000 patients following surgery

Candida species account for 78 percent of all nosocomial fungal infections
Sepsis and infection in ICU patients from an international multicentre cohort study

$N = 14,364$

Non infected patients $N = 11,330 \ (78.9\%)$
- ICU-acquired 15%

Already infected patients $N = 3,034 \ (21.1\%)$
- ICU-acquired 26%

Source of infection: Candida, fungi 11%

Early diagnosis of candidiasis in non-neutropenic critically ill patients

N = 3389

Candida 145/3389 (4.3%) [albicans 87%]
- invasive 120/145 (83%)
- colonisation 25/145 (17%)
- candidemi 24/145 (16%)
- endophthalmitis (3/145) (2%)

Mortality
67/145 (46%) – 51/145 (35%) died in the ICU

Journal of infection 2004; 48: 181-192
Mortality at ICU with and without fungal infections

Empiric therapy

Therapies for invasive candidiasis include:
- Amphotericin B (nephrotoxicity)
- Azoles – Fluconazole (Resistant strains C. glabrata, C. krusei)
- Caspofungin (compounds with favorable safety profile and active against C. glabrata and C. Krusei)
- Combination therapy

Duration of therapy
- Candidemia, 14 days after last positive blood culture
- Invasive fungal infections, 14 days

The key to successful treatment lies in the early identification and aggressive treatment of patients at high risk for infection.
Response rates for *Candida* species isolates from patients with invasive Candidiasis

<table>
<thead>
<tr>
<th>Species</th>
<th>Caspofungin</th>
<th>Amphotericin B</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>C. albicans</em></td>
<td>64% (23/36)</td>
<td>58% (34/59)</td>
</tr>
<tr>
<td><em>C. glabrata</em></td>
<td>77% (10/33)</td>
<td>80% (8/10)</td>
</tr>
<tr>
<td><em>C. tropicalis</em></td>
<td>85% (17/20)</td>
<td>71% (10/14)</td>
</tr>
<tr>
<td><em>C. krusei</em></td>
<td>100% (4/4)</td>
<td>0% (0/1)</td>
</tr>
</tbody>
</table>

Combinations - Candida infections
if 1 is good, 2 or more must be better

No difference in sickest or healthy patients

Voriconazole versus a regiment of amphotericin B followed ny floconazole for candidaemia in non-neutropenic patients: a randomised multicenter trial.
N=370 patients were included.
Treatment of fungal infections in the surgical ICU

*Positive blood culture:* If the patient is hemodynamic stable:
Fluconazole 800 mg initially, then 400 mg/day for about 14 days.
If the patient is hemodynamic labile: Caspofungin 70 mg x 1 followed by 50 mg daily
or Liposomal Amphotericin B 3 mg/kg/day or Voriconazole 6 mg/kg every 12 h for
24 h, anf then at 3 mg/kg every 12 h. Duration of treatment about 14 days.

*Negative blood culture:* Candida species are isolated from at least 2 foci.
Fluconazole 800 mg initially followed by 400 mg daily for subsequent
14 days.

*Candida* spp. not sensitive to Fluconazole, e.g. *C. glabrata* and *C. krusei* must be treated
with a different therapeutic approach, e.g. Caspofungin, new Azole antifungals,
Liposomal Amphotericin B.

Candida species are only isolated from one anatomical location.
Observation without treatment.
Prophylactic therapy

The goal of preventive therapy is to offer effective antifungal control on high-risk patients while minimizing the frequency of toxic side effects and development of antifungal resistance.
Randomized, doubleblind placebo-controlled study among high-risk surgery patients

High-risk patients:
Patients with recurrent gastrointestinal perforation or anastomotic leakage (ICU patients). Fluconazole: 400 mg/day i.v. N = 23

<table>
<thead>
<tr>
<th></th>
<th>Fluconazole</th>
<th>Placebo</th>
<th>P</th>
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<tbody>
<tr>
<td></td>
<td>N = 23</td>
<td>N = 20</td>
<td></td>
</tr>
<tr>
<td><strong>APACHE II</strong></td>
<td>13 (4 – 24)</td>
<td>13 (16 – 24)</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Candida in peritoneal fluid</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- at study entry</td>
<td>10 (43)</td>
<td>7 (35)</td>
<td>NS</td>
</tr>
<tr>
<td>- during study</td>
<td>7 (30)</td>
<td>14 (70)</td>
<td>0.01</td>
</tr>
<tr>
<td>- emergence</td>
<td>2/13 (15)</td>
<td>8/13</td>
<td>0.04</td>
</tr>
<tr>
<td><strong>Over all mortality</strong></td>
<td>7 (30)</td>
<td>10 (50)</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Death due to intra-abdominal candidiasis</strong></td>
<td>0</td>
<td>4 (20)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Prophylaxis against Candida peritonitis

2005

2006
Mortality
Systemic antifungal vs placebo/no antifungal

<table>
<thead>
<tr>
<th>Fluconazole, 7 trials</th>
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</thead>
<tbody>
<tr>
<td>Ketoconazole 4 trials</td>
</tr>
<tr>
<td>2000 - 2003</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Antifungal</th>
<th>Control</th>
<th>(P)</th>
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<tr>
<td>149/664</td>
<td>213/836</td>
<td>0.03</td>
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Playford EG, et al. The Cochrane Library 2006
**Proven invasive fungal infection**

Systemic antifungal vs placebo/no antifungal

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<thead>
<tr>
<th></th>
<th>Antifungal</th>
<th>Control</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluconazole, 8 trials</td>
<td>33/545</td>
<td>79/715</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Ketoconazole 2 trials</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2000 - 2003</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Playford EG, et al. The Cochrane Library 2006
Proven invasive fungal infection (azole-resistant Candida species)  
Systemic antifungal vs placebo/no antifungal

Fluconazole, 6 trials  
Ketoconazole 1 trial  
2000 - 2003

<table>
<thead>
<tr>
<th>Antifungal</th>
<th>Control</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>5/401</td>
<td>9/401</td>
<td>$= 0.4$</td>
</tr>
</tbody>
</table>

Playford EG, et al. The Cochrane Libary 2006
The use of topical nonabsorbable gastrointestinal antifungal prophylaxis to prevent fungal infections in critically ill immunocompetent patients.

- Systematic review and meta-analysis of 9 randomized clinical trials with a total of 1,226 patients. 7 studies double blind
- Ketoconazole or fluconazole vs placebo or no treatment

<table>
<thead>
<tr>
<th></th>
<th>Treatment</th>
<th>Controls</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Candidemia</td>
<td>0.9 (4/408)</td>
<td>4.5 (26/567)</td>
<td>0.002</td>
</tr>
<tr>
<td>Mortality attributable to Candida</td>
<td>0.7 (2/278)</td>
<td>3.4 (15/437)</td>
<td>0.019</td>
</tr>
</tbody>
</table>

Antifungal agents for preventing fungal infection in non-neutropenic critically ill and surgical patients.

- Systemic review and meta-analysis of 1606 randomized patients
- Fluconazole or Ketoconazole vs. placebo or no treatment

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<thead>
<tr>
<th></th>
<th>Treatment</th>
<th>Controls</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proven invasive fungal infections</td>
<td>0.06 (33/545)</td>
<td>0.11 (79/715)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Total mortality</td>
<td>0.22 (149/664)</td>
<td>0.25 (213/836)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Despite trials of antifungal prophylaxis for patients in surgical intensive care units had problems in design:

Prophylaxis against Candida should ”probably” be given to high-risk G-I patients (re-operation for severe intraabdominal infection).


Prophylaxis against Candida should probably be given to high-risk G-I patients (re-operation for severe intraabdominal infection and severe peritonitis).
Conclusion - Prophylaxis

Cumulative evidence from randomized placebo-controlled trials indicates that antifungal prophylaxis can reduce the incidence of invasive candidiasis in high-risk patients and patients undergoing organ transplantations.

The different studies have shown fluconazole prophylaxis to reduce the incidence of intra-abdominal candidiasis in high-risk patients (recurrent perforation, anastomotic leakage).

Duration of prophylactic therapy: 12 days

Within the last 2 years 5 studies have further confirmed this statement.
## Meta-analysis, Fluconazole

<table>
<thead>
<tr>
<th>Research Team</th>
<th>Initially</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ables et al</td>
<td>800 mg/day (400 mg/day)</td>
<td>Until ICU discharge</td>
</tr>
<tr>
<td>Eggimann et al</td>
<td>400 mg/day</td>
<td>15 days</td>
</tr>
<tr>
<td>Garbino et al</td>
<td>100 mg/day</td>
<td>Until withdrawal of mechanical ventilation</td>
</tr>
<tr>
<td>He et al</td>
<td>100 mg/day</td>
<td>Until ’relief of predisposing condition’</td>
</tr>
<tr>
<td>Jacobs et al</td>
<td>200 mg/day</td>
<td>During septic condition</td>
</tr>
<tr>
<td>Parizkova et al</td>
<td>100 mg/day</td>
<td>Until ICU discharge</td>
</tr>
<tr>
<td>Petz et al</td>
<td>800 mg/day (400 mg/day)</td>
<td>Until ICU discharge</td>
</tr>
</tbody>
</table>
Mortalitet

Reoperation: severe peritonitis

+ ICU: 32%
+ ICU + dialysis no sepsis: 45%
+ ICU + dialysis + sepsis: 70%
+ ICU + Candida infection: 50%
+ ICU + Aspergillus: 65%
+ ICU + fungal infection + dialysis > 70%