Fungal infections in non-neutropenic surgical patients

Risk factors

Candida infections

Therapy and prophylaxis

Conclusions

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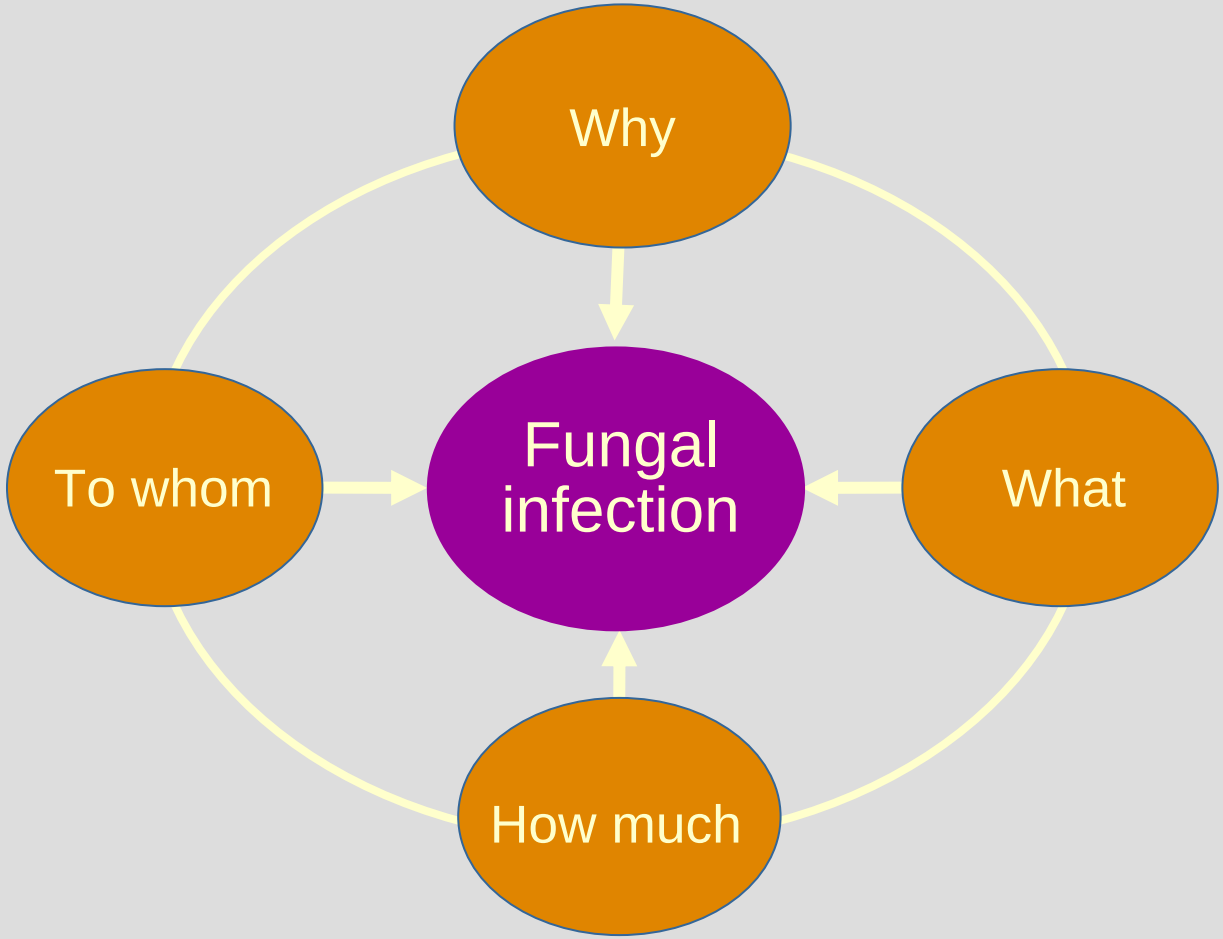
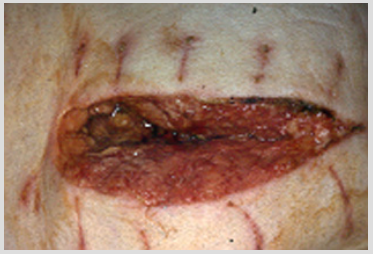

Why
To whom
Fungal infection
What
How much

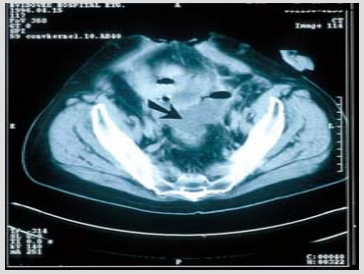
No. of operations/year

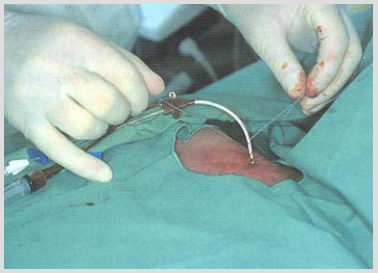
- **330.000 operations**
- **60.000 intraabdominal operations**

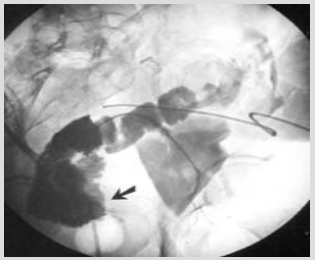
- **4% at ICU = 2400 patients**
- **Non-neutropenic critically ill patients**

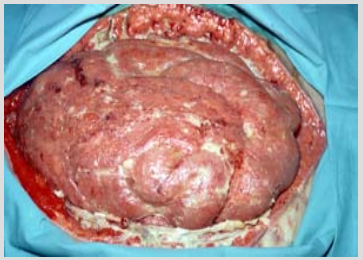
Intra-abdominal infections











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**

Alberti C, et al. Intensive Care Med 2002; 28:108-121
Calanda T and Marchetti. CID 2004; 39 (Suppl 4) 185-92.

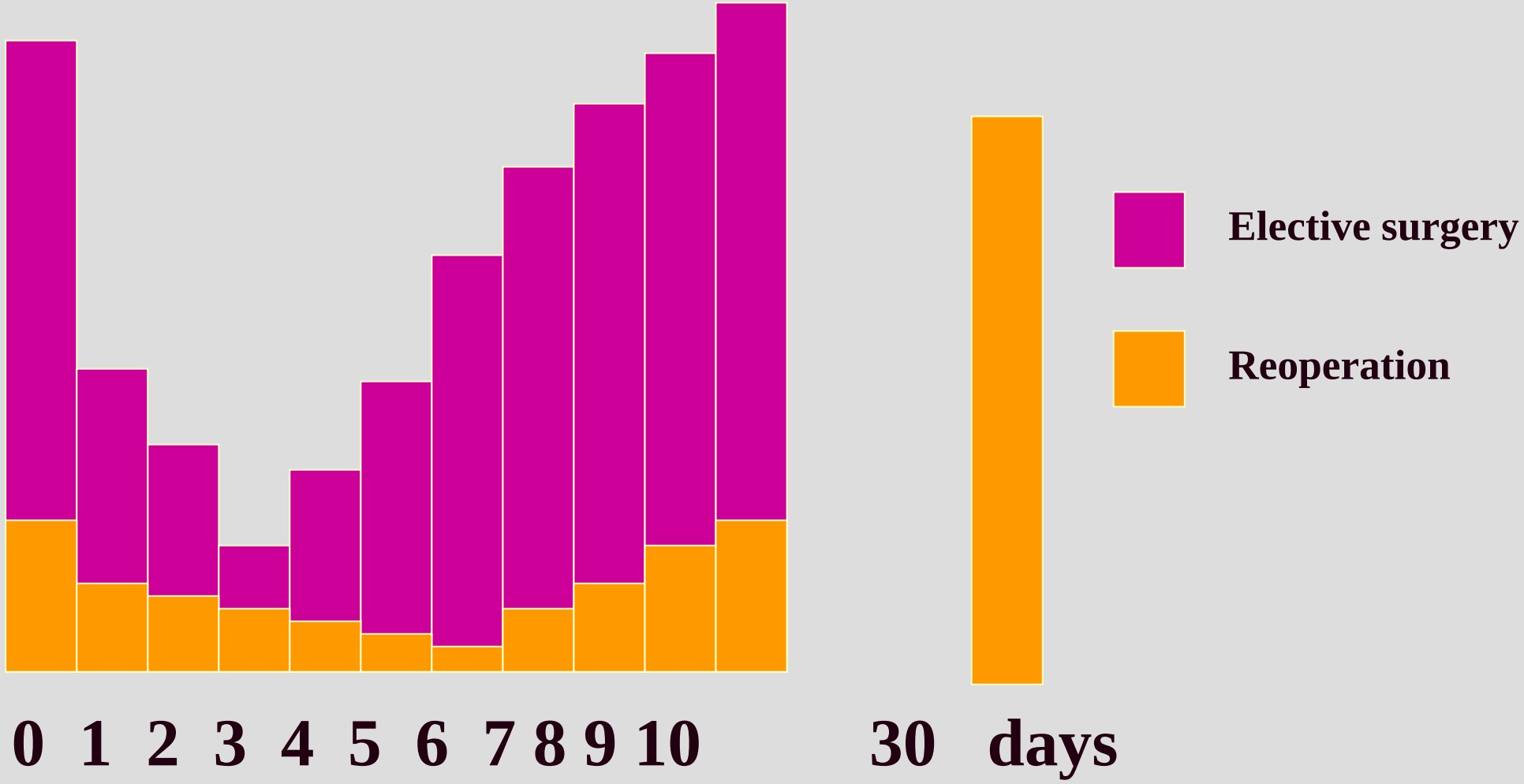
G-I tract

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

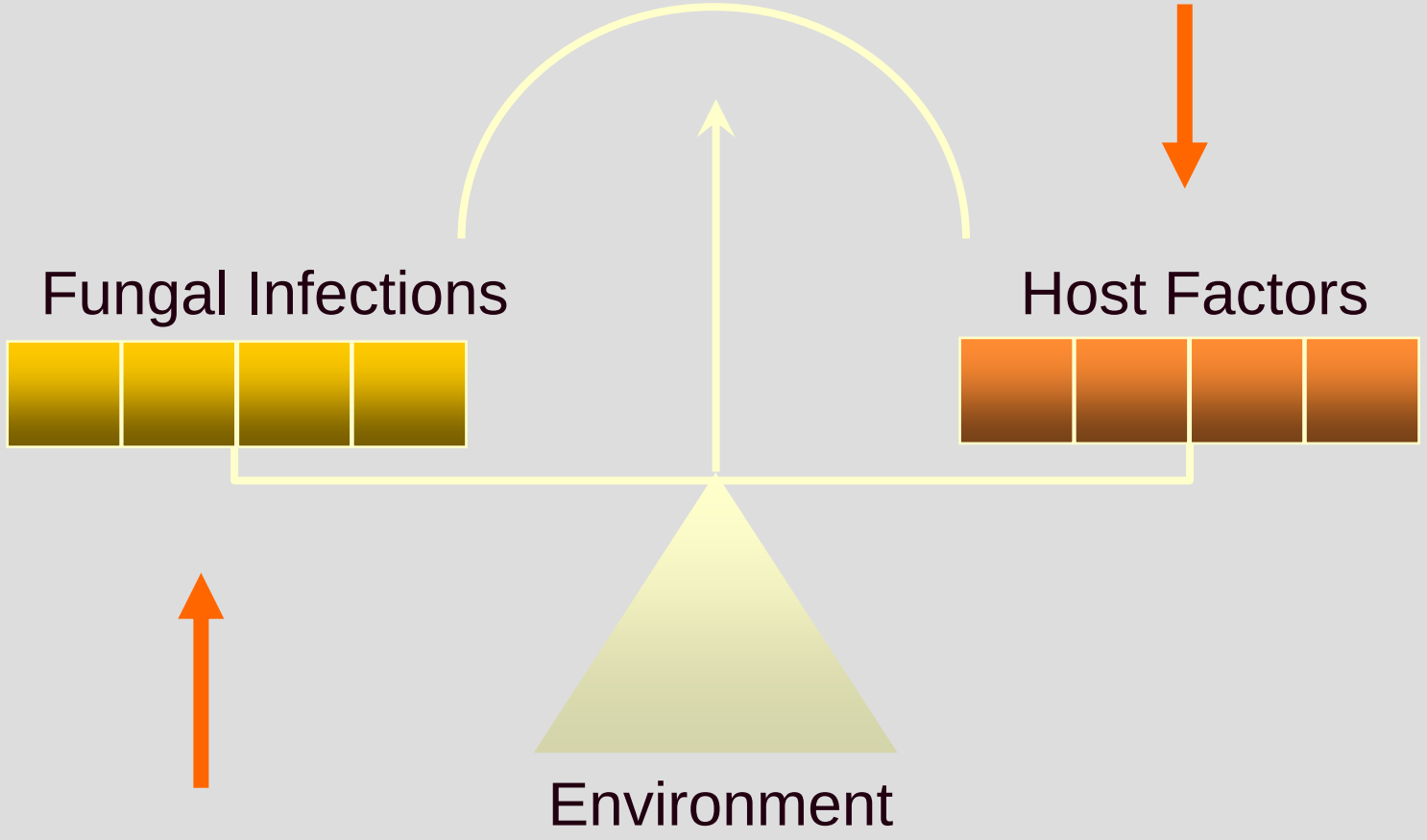
- **If *Candida* is not cleared from the peritoneal cavity, seeding results in the development of intra-abdominal *Candida* infection.**

Lippsett PA. linical trials of antifungal prophylaxis among patients in surgical intensive care units. CID 2004; 39 (Suppl 4): 193 - 8.

Immune reaction

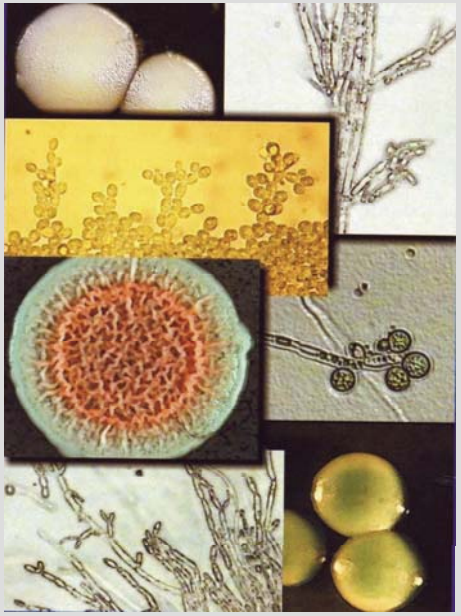


Change in balance between health and disease

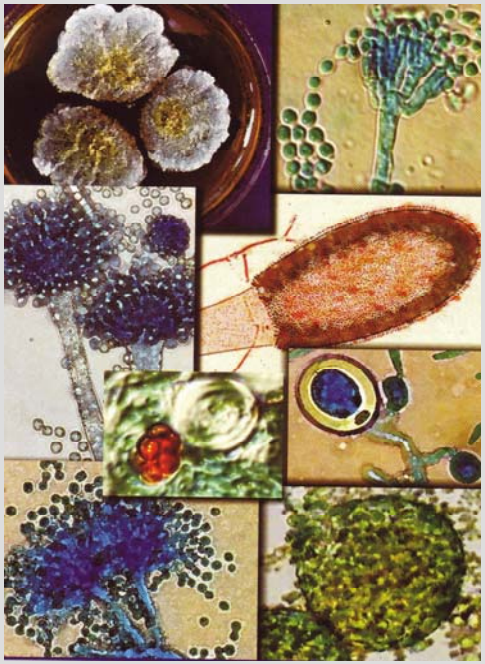


Fungi main players

- Yeast
  - **Candida**
  - **Cryptococcus**



- Mould
  - **Aspergillus**
  - Mucormycosis (zygomycosis)



Candida infections

- **Candida affects high-risk patients who are eighter 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 nosocomiel 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, particulary to C. glabrata (20%), C. trophicalis (4%) and C. krusei (3%)**
- **Until recently few randomized trials**

Arendrup MC et al. Journal of Clin Microbiol 2005;43:4434-40.

Aspergillus

Common cause of invasive fungal infection in neutropenic patients

- **Species:** **A. Fumingatus**
  A. Niger
  A. Flavus
  A. Glaucus

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

Maertens J, et al. Clinical Infectious Disease 2004; 39: 1563-71

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%

Intensive Care Med 2002;28:108-121.

Early diagnosis of candidiasis in non-neutropenic critically ill patients

N = 3389

Candida 145/3389 (4.3%) [albicans 87%]

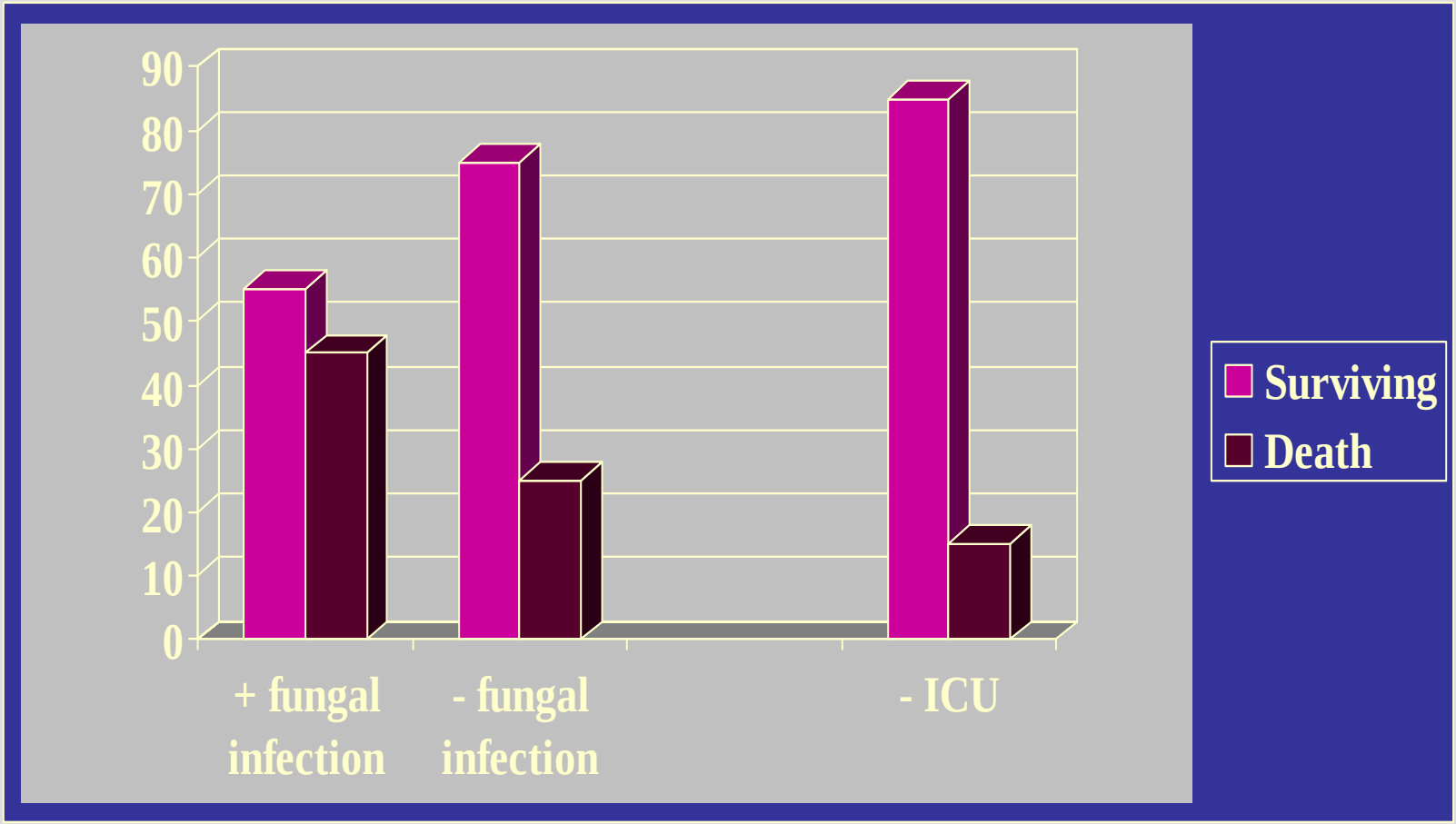
- **invasive 120/145 (83%)**
- **colonisation 25/145 (17%)**
- **candidemi 24/145 (16%)**
- **endopthalmitis (3/145) (2%)**

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



Heslet L, Moesgaard F, Tvede M. Yearbook of intensive care and emergency medicine 2001; p. 162-74.

Empiric therapy

Therapies for invasive candidiasis include:

- **Amphoteracin 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 succesful 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

Species	Caspofungin	Amphotericin B
C. albicans	64 % (23/36)	58% (34/59)
C. glabrata	77% (10/33	80% (8/10)
C. tropicalis	85 (17/20)	71% (10/14)
C. krusei	100 4/4	0 (0/1)

NEJM 2002; 347: 2020 – 29.

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

No difference in sickest or healthy patients

Rex JH, et al. Clin infect Dis 2003;36:1221-28.

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.

Kullberg BJ, et al. www.thelancet.com October 12, 2005

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, Liposomale Amphotericin B.**

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

Prophylaxtic 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

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

Eggimann P, et al. Crit Care Med 1999;27:1066-72

Prophylaxis against Candida peritonitis

2005

Shorr AF, et al. Crit Care Med 2005; 33: 1928-35 (Meta-analysis, USA)

Silvestri L, et al. Intensive Care Med 2005; 31: 898-910 (Meta-analysis, Italy, UK)

Ho Ming Ho, et al. Crit Care Med 2005; 33: 2383-92 (Meta-analysis, Australia)

Cruciani M, et al. Intensive Care Med 2005;31:898-910 (Review of randomized controlled trials, Italy, UK).

2006

Montravers P, et al. Crit Care Med 2006; 34: 646-52 (Retrospective study on peritonitis, France)

Playford EG, et al. Cochrane Database Syst Rev 2006 Jan 25 (Australia)

J Antimicrob Chemother 2006; 57: 628-38 (Metanalysis, Australia).

Mortality

Systemic antifungal vs placebo/no antifungal

Fluconazole, 7 trials **Ketoconazole 4 trials** **2000 - 2003**		
Antifungal	**Control**	***P***
149/664	**213/836**	**0.03**

Playford EG, et al. The Cochrane Libary 2006

Proven invasive fungal infection

Systemic antifungal vs placebo/no antifungal

Fluconazole, 8 trials **Ketoconazole 2 trials** **2000 - 2003**		
Antifungal	**Control**	***P***
33/545	**79/715**	**< 0.0001**

Playford EG, et al. The Cochrane Libary 2006

Proven invasive fungal infection (azole-resistant Candida species)

Systemic antifungal vs placebo/no antifungal

Fluconazole, 6 trials **Ketoconazole 1 trial** **2000 - 2003**		
Antifungal	**Control**	***P***
5/401	**9/401**	**= 0.4**

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

	Treatment	**Controls**	***P***
Candidemia	**0.9 (4/408)**	**4.5 (26/567)**	**0.002**
Mortality attributable to *Candida*	**0.7 (2/278)**	**3.4 (15/437)**	**0.019**

Mario Cruciani et al. Intensive Care Med 2005; 31: 1479 -1487

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

	Treatment	Controls	*P*
Proven invasive fungal infections	**0.06 (33/545)**	**0.11 (79/715)**	**0.0001**
Total mortality	**0.22 (149/664)**	**0.25 (213/836)**	**0.03**

E. Geoffrey Playford et al. J Antimicrob Chemother 2006;57:628-38.

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).

But after 4 meta-analysis and Playford EG, Webter AC, Sorrel TC, Craig JC. Antifungal agents for preventing fungal infections in non-neutrogenic critically ill and surgical patients: systematic review and meta-analysis of randomised clinical trials. J Antimicrob Chemother 2006; 57: 628-38.

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 hig-risk patients and patients undergoing organ transplantations.

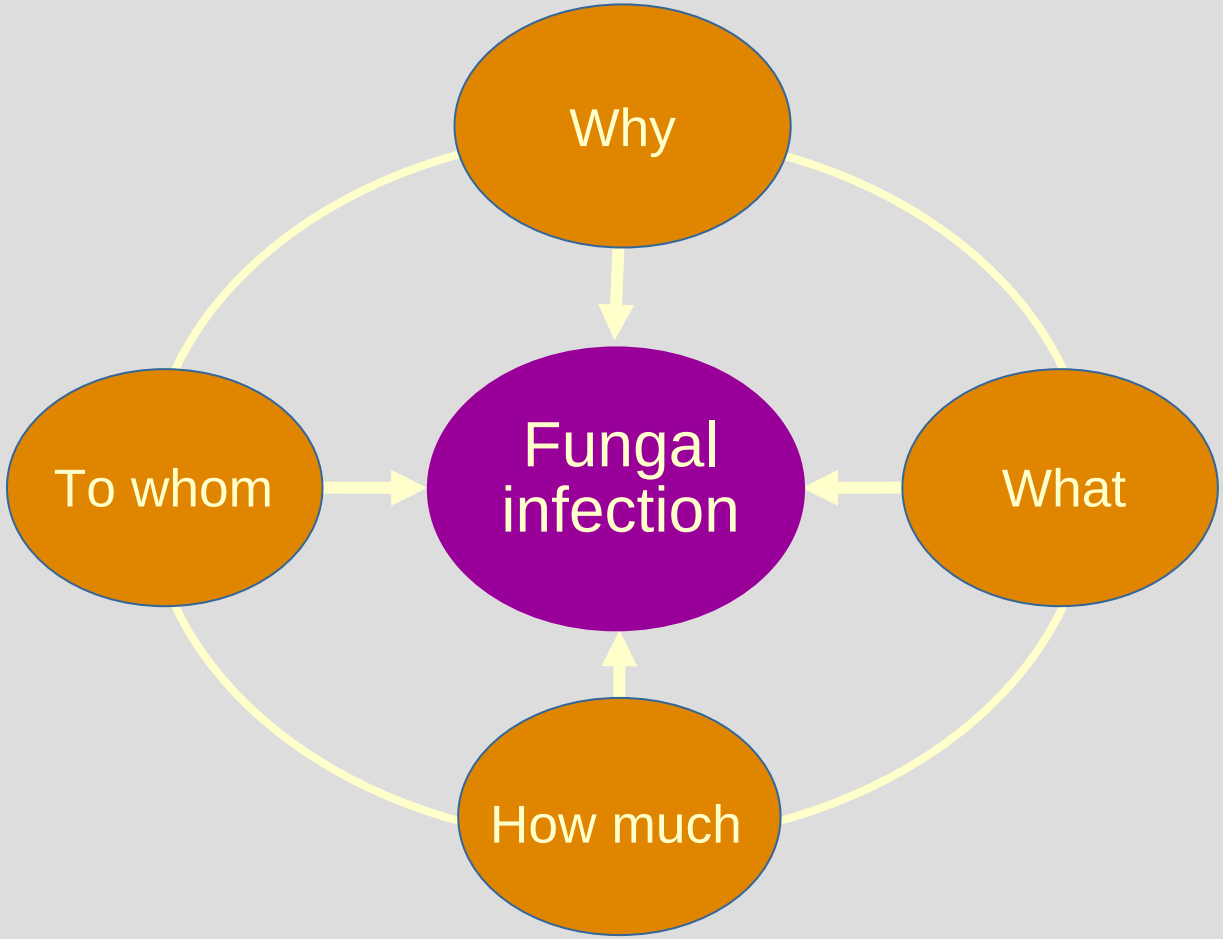
The different studies have shown fluconazole prophylaxis to reduce the incidence of intra-abdominal candidiasis in high-risk patients (recurrent perforation, anastomotic leakage).

Duration of prophylactic therapy: 12 days

Eggimann P, et al. Crit Care Med 1999;27:166-1072.
Petz RK, et al. Ann Surg 2001;233:542-48.
Garbino J, et al. Intensive Care Med 2002;28:1708-17.
Within the last 2 years 5 studies have further confirmed this statement.

Meta-analysis, Fluconazole

	Initially	Duration
Ables et al	800 mg/day (400 mg/day)	Until ICU discharge
Eggimann et al	400 mg/day	15 days
Garbino et al	100 mg/day	Until withdrawal of mechanical ventilation
He et al	100 mg/day	Until ’relief of predisposing condition’
Jacobs et al	200 mg/day	During septic condition
Parizkova et al	100 mg/day	Until ICU discharge
Petz et al	800 mg/day (400 mg/day)	Until ICU discharge


Why
To whom
Fungal infection
What
How much

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%