

# Importance of fungal infections in the surgical ICU

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# Preliminary remarks

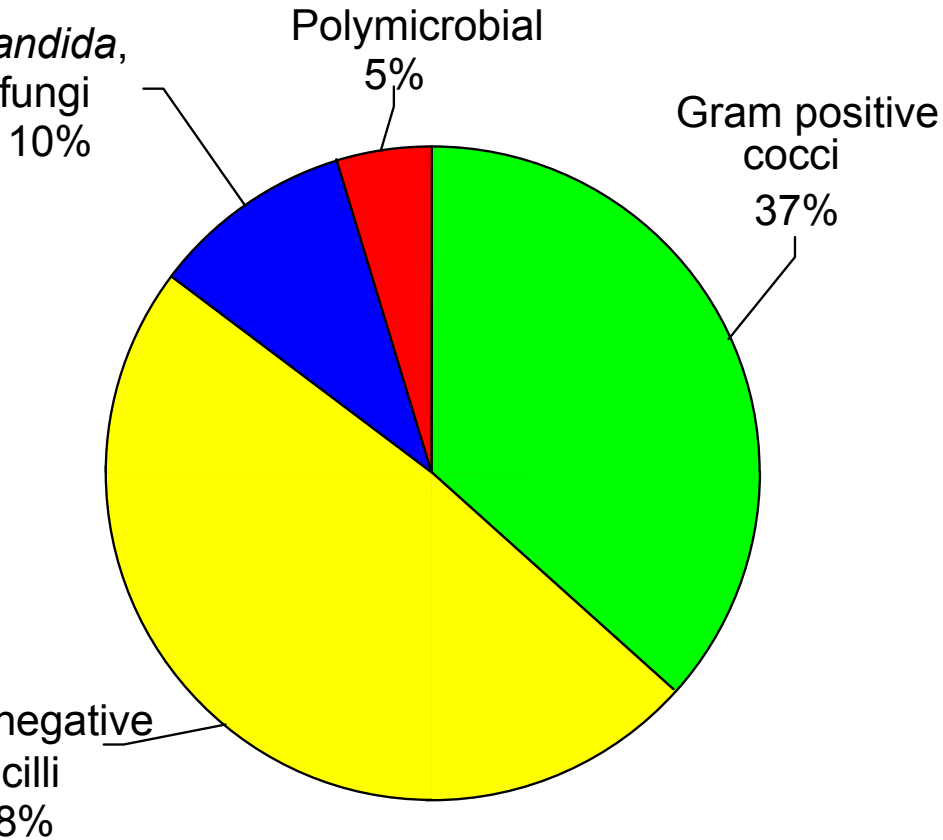
Few specific studies

Mixed units / mixed populations

No therapeutic trial

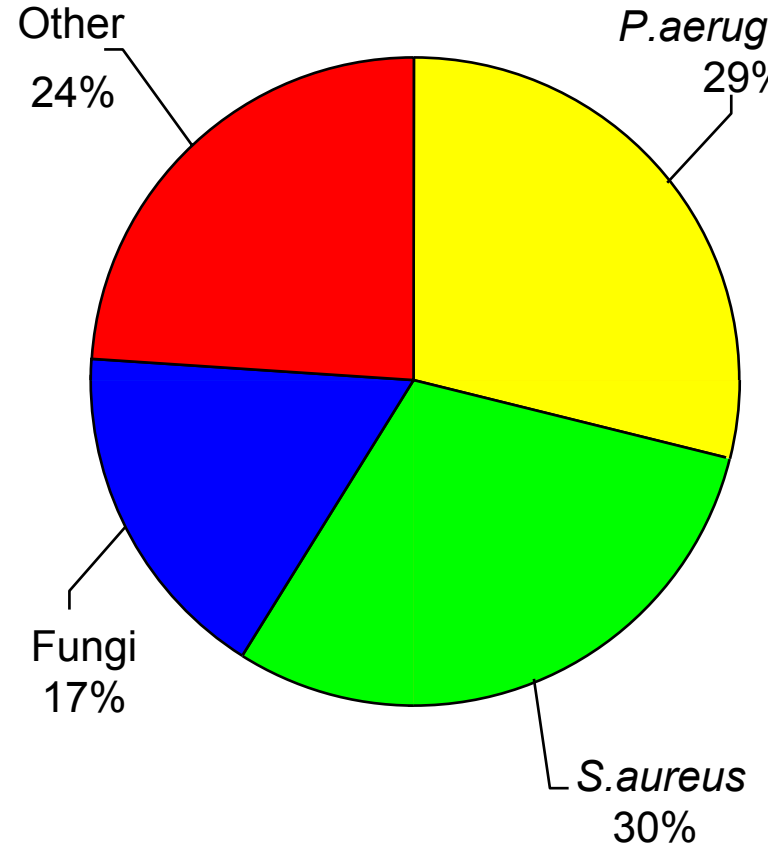
# Prevalence of fungal infections

One year patients with sepsis  
28 ICUs ; 8 countries ; 1,581 pts



Alberti C. *Intensive Care Med* 2002;28:108

One day - nosocomial infections  
1,417 ICUs ; 17 countries ; 2,064 pts



Vincent JL. *JAMA* 1995;274:

# Epidemiology of fungal infections

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Yeasts and molds

Candida >80% of all fungi isolates  
causing nosocomial infections

Aspergillus spp

Emerging fungal pathogens (fusarium, rhizopus spp.)

*Trick WE et al. Clin Infect Dis 2002;35:627*

*Beck-Sague CM et al. J Infect Dis 1993;167:12*

*CDC. Am J Infect Control 2003;31:481*

# Risk factors of invasive aspergillosis in IC

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Bone marrow transplantation

Hematologic malignancies

Immunosuppressive therapy

    Solid organ transplantation (liver, kidney)

    Systemic disease

COPD

Liver cirrhosis

east infections in surgical ICU patients

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epidemiology

therapeutic issues in ICU patients

# Prevalence and source of Candida infections in surgical ICU

	Cohort	Infections	Incidence	Blood	Peritoneum	UTI	S
	N=	N=	%	%	%	%	%
Arbino et al	110	16	12	42	17	25	14
Arbino et al	117	14	11.9	29	36	21	14
Arbino et al	409	7	1.7	29	71	-	-
Petri et al	650	11	1.7	81	-	-	-

Arbino J et al. *Clinical Nutrition* 2004;23:705

Arbino J et al. *J Intensive Care Med* 2000 ;15 :255

Petri MG et al. *Intensive Care Med* 1997;23:751

Pittet D et al. *Ann Surg* 1994;220:751

# Incidence of Candidemia in ICU pts

		/1,000 admissions	/10,000 days	Type of unit
orano	<i>J Hosp Infect 2004;57:8</i>	2.6	3.3	mixed ICUs
	<i>Am J Med 2002;113:480</i>	2.5	-	mixed ICUs
mberg	<i>Clin Infect Dis 2001;33:177</i>	9.81	9.8	surgical ICU
gel-Frausto	<i>Clin Infect Dis 1999;29:253</i>	9.8	9.9	surgical ICU
nert	<i>Infection 2000;28:26</i>	6.06	-	mixed ICUs
bino	<i>Medicine 2002;81:425</i>	1.12	2.8	mixed ICUs
as Salas	<i>Intensive Care Med 1997;23:23</i>	2.0	-	mixed ICUs
k	<i>Clin Infect Dis 2002;35:627</i>	-	4.8	mixed ICUs
eu	<i>J Crit Care 2002;17:168</i>	3.1	22	mixed ICUs

# Fungal species isolated from blood stream infection in ICU

	Blot (n=57)	Blumberg (n=42)	Nolla-Salas (n=47)	Swoboda (n=73)	Tortorano (n=28)	Trick (n=275)
	S,M,C,BICU	SICU	M,SICU	SICU	M,SICU	All type
<i>Candida</i>	72	48	60	44	54	59
<i>Aspergillus</i>	26	24	2	30	3	12
<i>Cryptosporidium</i>	2	7	17	8	29	11
<i>Trichosporon</i>	-	19	8	7	3	10
<i>Trichosporon</i>	-	-	2	6	-	1.2
Other	-	2	11	6	11	7

Expressed as proportions of the total number of isolates

S: surgical; M: medical; C: cardiac; B: burned patients

Blot S. *J Hosp Infect* 2001;47:308

Blumberg HM. *Clin Infect Dis* 2001;33:177

Nolla-Salas. *J Intensive Care Med* 1997;23:23

Swoboda SM. *Surg Infect (Larchmt)* 2003;4:345

Tortorano AM. *J Hosp Infect* 2004;57:8

Trick WE. *Clin Infect Dis* 2002;35:627

# Variability between centers

Number of episodes and incidences of candidemia in 2000

Report of 17 surveyed Swiss tertiary care hospitals

Patient location	University		University affiliated	
	No. of episodes	Incidence <sup>a</sup>	No. of episodes	Incidence <sup>a</sup>
ICU	23	1.9 (0.91–6.7)	7	0 (0–9.36)
Medical	9	2.5 (1.67–13.3) <sup>h</sup>	3	0 (0–12.3)
Surgical	13	2.86 (0–12)	4	0 (0–12.5)
Pediatric <sup>i</sup>	1	0 (0–0.5)	0	0

Data are median no. of episodes per 10,000 patient-days (range).

# Variability between type of units

1989-1999                      311 hospitals                      1,116 ICUs  
3,041,585 patients  
2,759 blood stream infections with candida species

Incidence of BSI expressed as number of BSIs per 10,000 CVC da

Medical ICUs	7.2
Pediatric ICUs	6.4
Surgical ICUs	4.9
Medical-surgical ICUs teaching hospitals	5.4
Medical-surgical ICUs non-teaching hospitals	4.5
Coronary ICUs	3.0
Cardiothoracic ICUs	2.4

# Risk factors of candidemia

Steroids	Age
Vascular access	Severity of disease
Candida colonisation	Length of stay
Antibiotics	Mechanical ventilation
Surgery	Multiple transfusion
G-intestinal bleeding	Parenteral nutrition
Bladder catheter	Anti H2
Renal failure	Antifungal prophylaxis

# Risk factors of candidemia

urgery	RR 7.3 (1-53.8) CI 95%
parenteral nutrition	RR 3.6 (1.8-7.5)
renal failure	RR 4.2 (2.1-8.3)
triple lumen catheter (previous surgery)	RR 5.4 (1.2-23.6)

*Blumberg HM. Clin Infect Dis 2001;33:177*

Candida colonisation	RR 10.64 (1.4-78.7)
	RR 4.64 (2.6-8.2)

*Pelz RK. Ann Surg 2001;233:542*

*Pittet D. Ann Surg 1994;220:751*

# Prevalence of resistant candida among ICU patients

## blood stream infections

% Susceptibility toward

	Amphotericin B	5-FC (nb of strains)	Fluconazole (nb of strains)
Blumberg	100	97 (34/35)	89 (31/35) C glabrata : 2/8 R (1 DDS) C albicans: 2/26 R ; C tropicalis : 1 R
Rocco	NA	NA	82 (31/38) C glabrata : 3 R ; C krusei : 1 R C albicans: 2 R ; C tropicalis : 1 R
Tortorano	100	100	97 (56/58) C glabrata : 1 R; 1 DDS

*Blumberg HM. Clin Infect Dis 2001;33:177*

*Rocco TR. Arch Surg 2000;135:160*

*Tortorano AM. J Hosp Infect 2004;57:8*

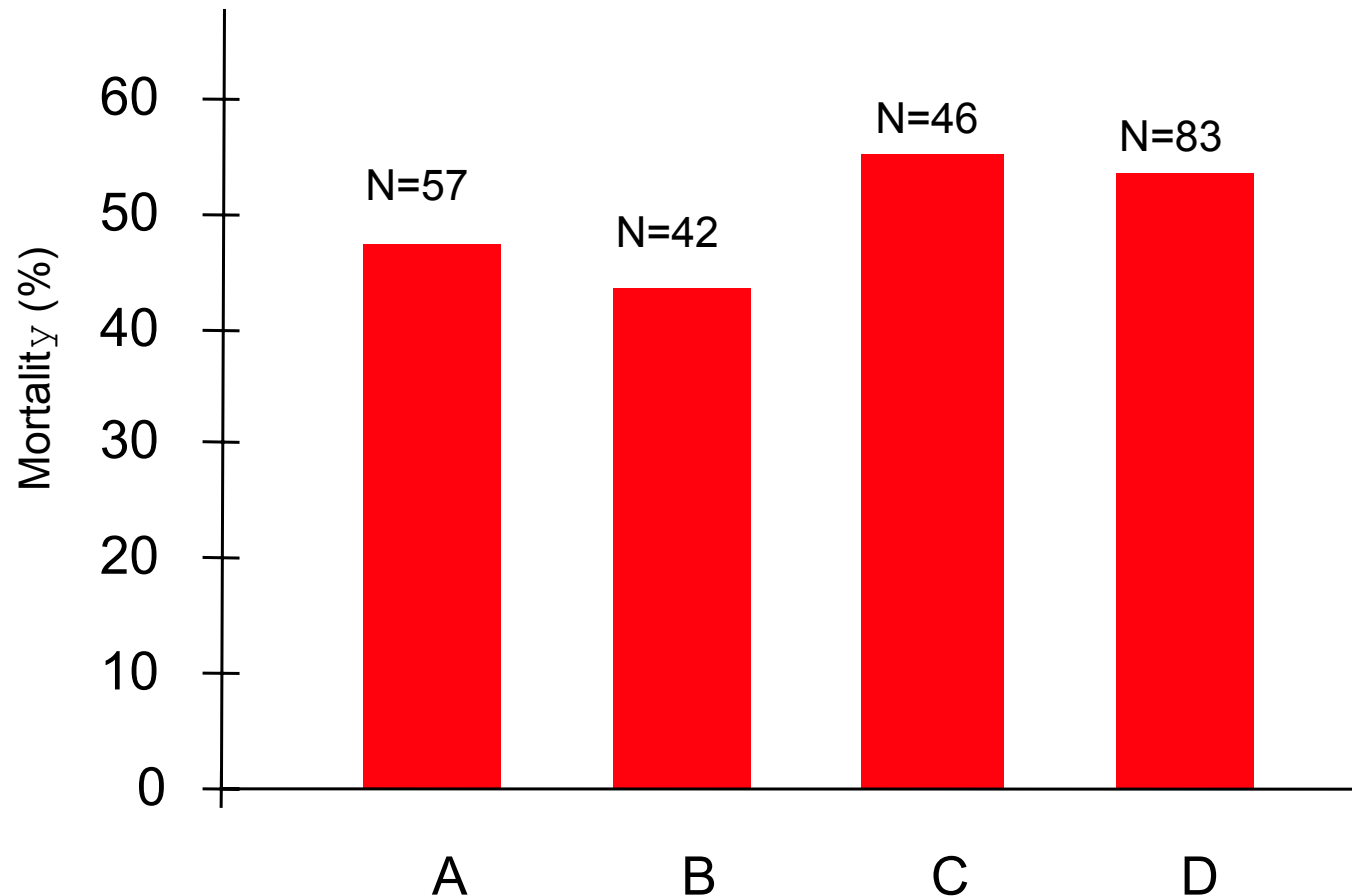
# Multiple organ dysfunction in candida infection

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Candidemia n= 42	%
Shock	60
Acute renal failure	55
DIC	45
ARDS	40

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# Prognosis of candidemia



A. Blot S. *J Hosp Infect* 2001;47:308

B. Blumberg HM. *Clin Infect Dis* 2001;33:177

C. Nolla-Salas J. *Intensive Care Med* 1997;23:23

D. Swoboda SM. *Surg Infect (Larchmt)* 2003;4:345

# Risk factors associated with ICU mortality in patients with candidemia

Variable	Odds ratio	[95% CI]	<i>P</i>
Age	1.05	[1.0-1.1]	0.02
Polymicrobial blood stream infection	5.37	[1.08-26.72]	0.04
Acute renal failure	4.66	[1.04-20.97]	0.04
ICU stay	0.97	[0.95-1.0]	0.09

*Blot S. J Hosp Infect 2001;4*

Variable	Odds ratio	[95% CI]
Broad spectrum antibiotics	69.7	[2.1-2351]
Fever	51.2	[2.4-1064]
Increased hospital length of stay	1.15	[1.04-1.25]
Post-transplantation	0.005	[0.0005-0.56]
Antifungal prophylaxis	0.29	[0.01-0.58]
Tight glucose control (<180 mg/dL)	0.3	[0.02-0.82]

*Swoboda SM. Surg Infect (Larchmt) 2003*

# Enterococci, Candida and Intraabdominal infection

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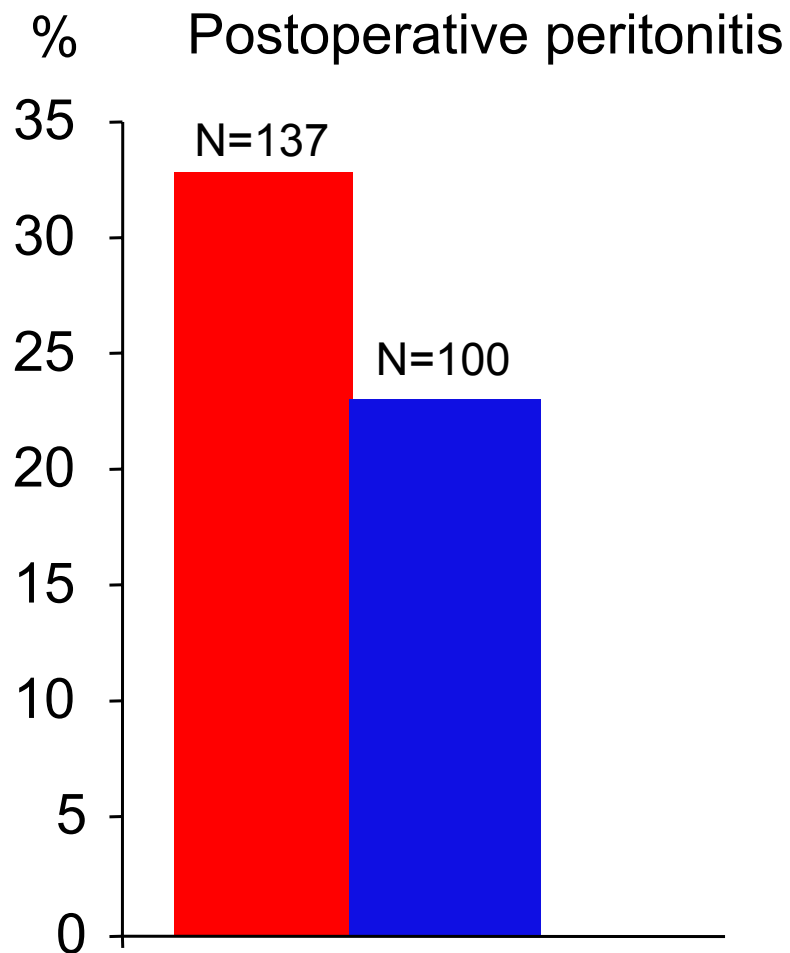
- Bowel commensals
- Low concentrations
- Low spontaneous pathogenicity
- Emergence following antibiotic therapy
- Source of debate on their pathogenic role

Candida peritonitis should be rephrased as

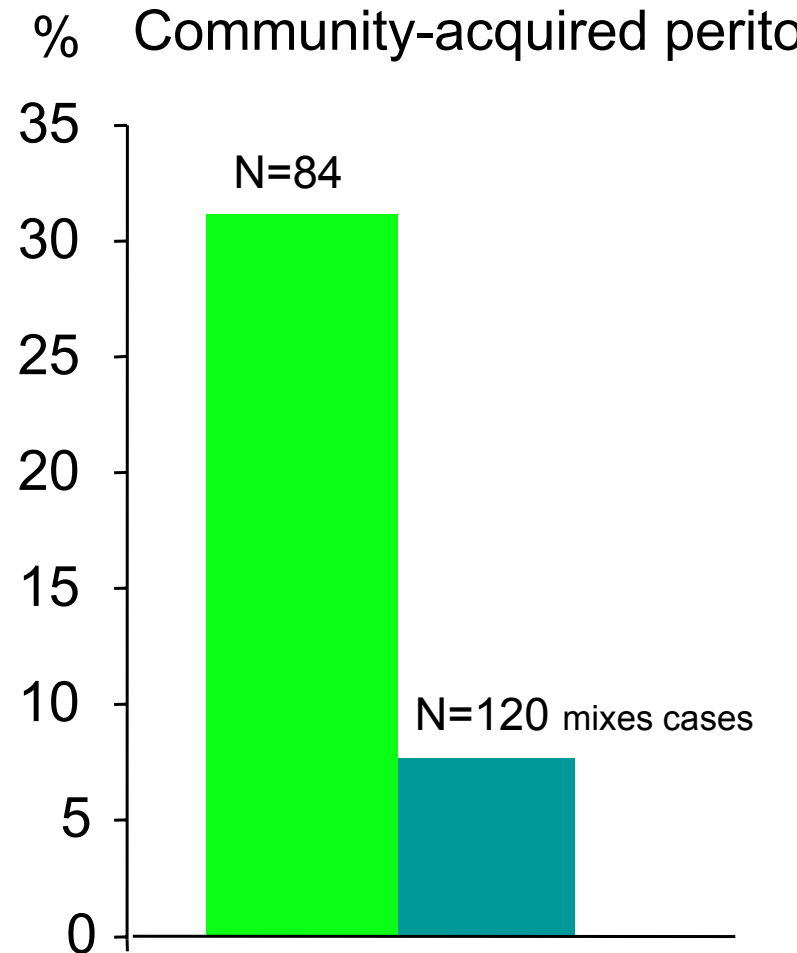
Extra-abdominal infections with positive culture of  
Candida

- Colonisation or infection
- Treatment or not

# Incidence of *Candida* peritonitis in ICU pts



Dupont H. *Crit Care Med* 2003;31:752  
Montravers P. *Clin Infect Dis* 1996;23:486



Dupont H. *Crit Care Med* 2003;31:752  
Sotto A. *J Antimicrob Chemother* 2002;50

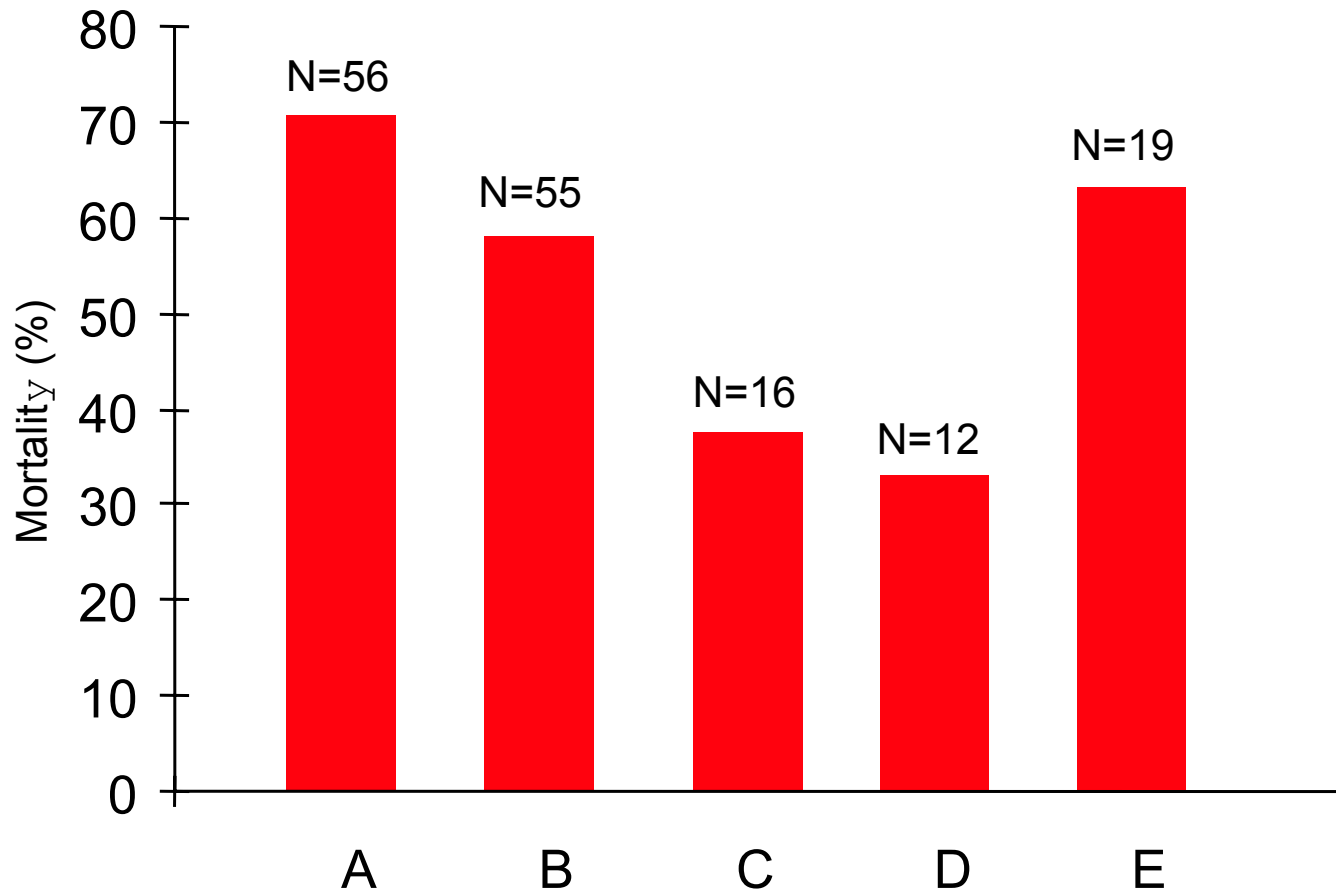
# Fungal species isolated from intraabdominal infection in ICU

	Dupont (n=85)	Eggimann (n=7)	Montravers (n=23)	Montravers (n=94)	Sandver (n=33)
	CAP/POP	POP	POP	CAP/POP	CAP
<i>C. albicans</i>	73	71	83	66	76
<i>C. glabrata</i>	18	14	4	16	15
<i>C. parapsilosis</i>	3	-	4	4	-
<i>C. tropicalis</i>	1	14	9	5	-
<i>C. krusei</i>	-	-	-	2	-
Miscellaneous	5	-	-	6	9

Expressed as proportions of the total number of isolates

POP: postoperative peritonitis ; CAP: community-acquired peritonitis

# Candida peritonitis and mortality



*A : Solomkin, Surgery 1980;88:524*

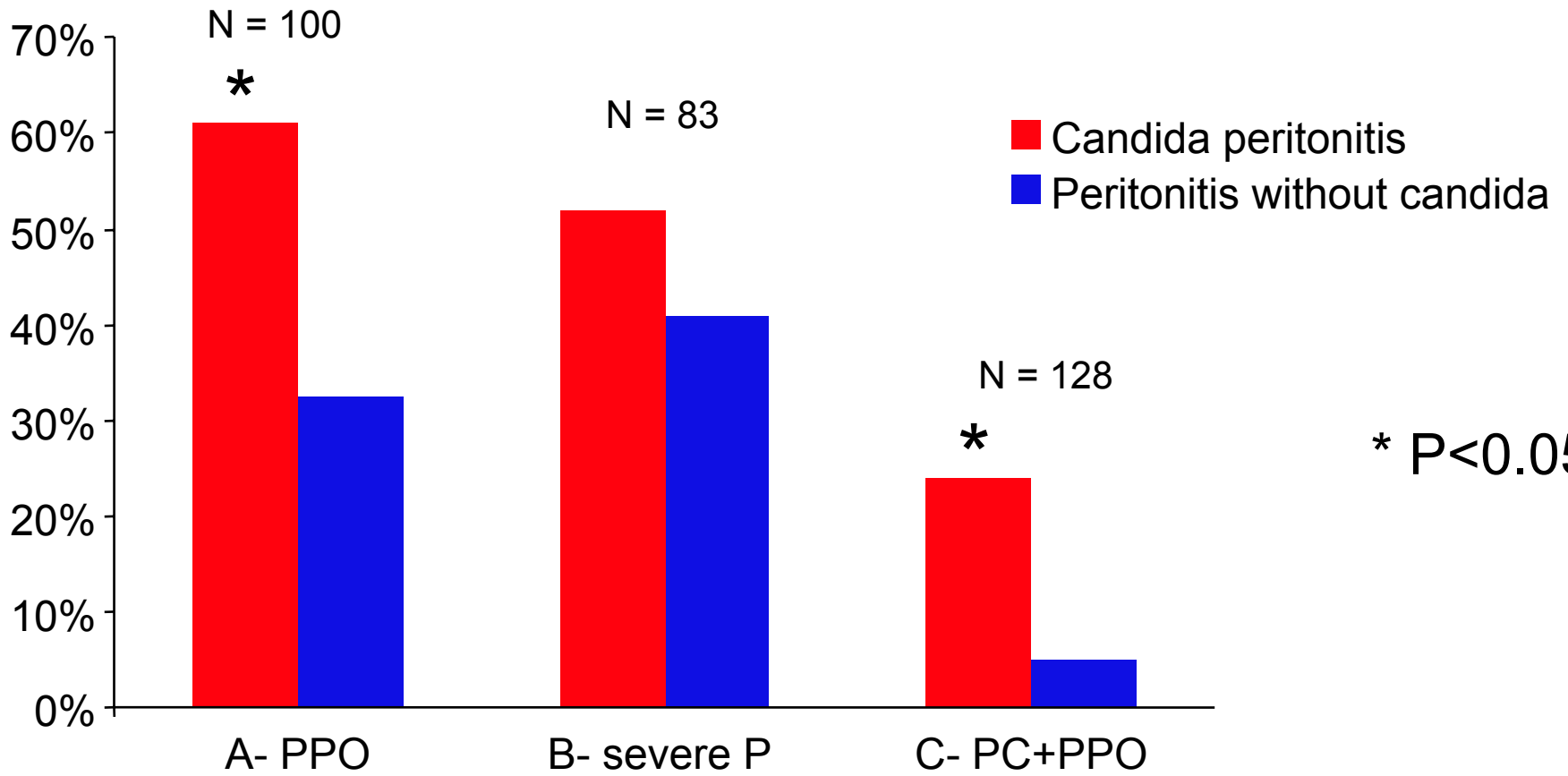
*B : Marsh, Ann Surg 1983;198:42*

*C : Alden, Am Surg 1989;55:45*

*D : Bayer, Am J Med 1976;61:832*

*E : Calandra T. Lancet 1989;ii:1437*

# Mortality of candida peritonitis in ICU



A : Montravers P. Clin Infect Dis 1996;23:486

B : Dupont H, Arch Surg 2002;137:1341

C : Sandven P. Crit Care Med 2002;30:541

# Candida a risk factor of death in peritonitis

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Case control study      ICU patients with peritonitis  
teaching and 3 non teaching hospitals

Matching criteria      Type of peritoneal infection (community-acquired/nosocomial)  
SAPS II score  
Age  
Year of hospitalisation

1997-2000

Cases with peritonitis and positive culture for Candida sp within peritoneal fluid

Control patients with peritonitis and without candida

# Candida as a risk factor of death in peritoniti

	Study Population		
	Cases	Controls	
ent reoperation	32 (35)	41 (24)	
n of mechanical ventilation, days	16 ± 17	11 ± 14 <sup>b</sup>	
of stay in ICU, days	23 ± 24	16 ± 16 <sup>b</sup>	
	34 (37)	45 (26)	
between index operation and death, days	22 ± 22	21 ± 34	
f death			
related to peritoneal infection	26 (29)	30 (18) <sup>a</sup>	
infectious cause	3 (3)	7 (4)	
infectious cause	2 (2)	7 (4)	

Risk Factors	Univariate Analysis		Multivariate Analysis	
	Odds Ratio (95% CI)	<i>p</i> Value	Adjusted Odds Ratio (95% CI)	<i>p</i>
roup	2.4 (1.2–4.6)	.01	3.0 (1.3–6.7)	
astrointestinal tract site	2.1 (1.1–4.1)	.02	4.9 (1.6–14.8)	
al antifungal treatment	1.9 (0.9–3.9)	.07	—	
ropriate empirical antibiotic treatment	2.2 (1.1–4.3)	.02	1.6 (0.6–4.3)	

# Risk factors associated with ICU mortality in patients with candida peritonitis

Variable	Odds ratio	[95% CI]	P
Apache II score >17	28.4	[5.7-142.5]	<.0
Respiratory failure	10.6	[2.2-51.2]	.0
Upper gastrointestinal tract origin	7.8	[1.7-34.7]	.0
Direct examination positive for candida	4.7	[1.2-19.7]	.0

# Predictive score of yeast isolation according to the grade of the score

Apache II score >17;

Respiratory failure

Direct examination positive for candida;

Upper Gastro intestinal tract origin

Grade A: no or one risk factor; Grade B: at least two risk factors

Grade C: at least three risk factors; Grade D: four risk factors

Score	Se (%)	Sp (%)	PPV (%)	NPV (%)	OA (%)
Grade A	3	100	40	100	40
Grade B	33	87	46	79	54
<b>Grade C</b>	<b>84</b>	<b>50</b>	<b>67</b>	<b>72</b>	<b>71</b>
Grade D	100	13	100	64	65

Se, sensitivity; Sp, specificity; PPV, predictive positive value; NPV, negative predictive value; OA, overall accuracy

# Treatment of candida peritonitis ?

not in Community-acquired infections

except in case of

immunosuppressive therapy for neoplasm

transplantation

inflammatory disease

necessary in postoperative or recurrent infection

# Treatment of candida peritonitis

C. albicans is found, fluconazole is an appropriate choice.

For fluconazole resistant Candida species, therapy with amphotericin B, caspofungin, or voriconazole is appropriate.

Caspofungin, or voriconazole cause substantially less toxicity than does amphotericin B and are specifically indicated for patients with renal dysfunction.

# Prevalence of resistant candida among ICU patients

tra-abdominal infections

% Susceptibility toward fluconazole

	C albicans	C glabrata	C parapsilosis	C tropicalis	Other Candida
Dupont	100 %	100 %	100 %	100 %	100 %
Sandven	100 %	20 % 4/5 DDS (MIC 16-32)	100 %	-	C norvegensis 2/2
Montravers	100 %	40 % 6/15 DDS	100 %	100 %	C krusei 2/2

*Dupont H, Arch Surg 2002;137:1341*  
*Sandven P. Crit Care Med 2002;30:3*  
*Montravers P. Crit Care Med 2006;3*

# Multiple organ dysfunction in candida infection

	Yeast + gp N=71	Yeast - gp N=150
PACHE II score	18 ± 7	17 ± 8
Organ system failure score	1.4±1.1	1.1±1.1*
Cardiovascular failure	66	48†
Renal failure	41	21
Respiratory failure	24	29

# Conclusion

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Surgical patients are at high risk for candida infections

Need for more studies in surgical cohorts

Renal dysfunction frequently associated

fluconazole is an appropriate choice

efficacy of new drugs to be assessed