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Terapia della candidiasi addomaniale

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INTRA ABDOMINAL CANDIDIASIS – open questions

a single definition gathering togheter different conditions

to treat or not to treat ?

empirical or targeted management ?

which role for biomarkers in the diagnosis?

which drugs ?

AN EXHAUSTIVE DEFINITION ?

Candida detection by direct microscopy or growth in culture from purulent or necrotic intra-abdominal specimens obtained during surgery or by percutaneous aspiration.

Candida growth from bile, intra-biliary duct devices, and biopsy of intra-abdominal organs.

Candida growth from blood during secondary and tertiary peritonitis in the absence of any other pathogen.

Candida growth from drainage tubes only if placed less than 24 h before the cultures become positive.

Candida as a risk factor for mortality in peritonitis

Montravers P et al, Crit Care Med, 2006

Design: A multiple-center, retrospective, case-control study conducted in ICU pts
Setting: 17 ICUs in teaching and nonteaching hospitals.
Patients: Cases were patients operated on for peritonitis with *Candida* cultured from the peritoneal fluid, whereas controls were operated patients free from yeast. Cases and controls were matched for type of infection, SAPS II, age, and time period of hospitalization.
Matching Process: 109 patients with a positive culture for *Candida* species in the peritoneal fluid obtained during surgery were selected as eligible cases for the study and 211 patients satisfying the inclusion criteria were selected as controls

	Study population			Nosocomial peritonitis		
	Cases	Controls		Cases	Controls	
Duration MV	16 ± 17	11 ± 14	<.01	18 ± 17	13 ± 16	<.01
Length of ICU stay	23 ± 24	16 ± 16	<.01	26 ± 25	18 ± 18	<.01
Death	37%	26%		48%	28%	<.05

Candida as a risk factor for mortality in peritonitis

Montravers P etal, Crit Care Med, 2006

Univariate and multivariate analysis with regard to deaths of pts with Nosocomial Peritonitis (*n* 164)

	Univariate analysis		Multivariate analysis	
RISK FACTORS	OR (95% CI)	p value	OR (95% CI)	p value
Case group (Candida +)	2.4 (1.2-4.6)	.01	3.0 (1.3-6.7)	.009
Upper GI tract site	2.1 (1.1-4.1)	.02	4.9 (1.6-14.8)	.005
Empirical antifungal Rx	1.9 (0.9-3.9)	.07	-	
Inappropriate ATB therapy	2.2 (1.1-4.3)	.02	1.6 (0.6-4.3)	.03

This study shows that isolation of Candida spp in peritoneal specimens of nosocomial peritonitis appears to be an independent risk factor for mortality.

Antifungal Therapy for Patients with Proven or Suspected Candida Peritonitis: Amarcand2, a prospective Cohort Study in French Intensive Care Units.

Montravers P et al, Clin Microbiol Infect. 2016 Oct 13.

ICU patients treated for CP were selected among the AmarCAND2 cohort, to compare patients receiving Early Antifungal Therapy (EAF/noCP) for not confirmed suspicion of CP to those with Early Antifungal Therapy with suspected secondarily confirmed CP (EAF/CP) or with primarily proven CP receiving Targeted Antifungal Therapy AF (TAF)

279 patients were evaluated (43.4% EAF/nonCP, 29.7% EAF/CP, and 25.8% TAF patients). At SAT initiation, the severity of illness was similar among EAF/nonCP and EAF/CP patients, lower among TAF patients (median SAPSII 49 and 51 vs. 35, respectively (p=0.001).

Candida albicans was involved in 67%, *Candida glabrata* in 15.6%. All strains were susceptible to echinocandin; 84% to fluconazole. Echinocandin was administered to 51.2% EAF/nonCP, 49% EAF/CP and 40% TAF patients.

At Day-28, 72%, 76% and 75% of EAF/nonCP, EAF/CP and TAF patients, respectively, were alive.

Only 56.6% of ICU patients receiving SAT had indeed CP. Most strains were susceptible to SAT.

Antifungal Therapy for Patients with Proven or Suspected Candida Peritonitis: Amarcand2, a prospective Cohort Study in French Intensive Care Units.

Montravers P et al, Clin Microbiol Infect. 2016 Oct 13.

Peritonitis score and *Candida* score were not helpful in this population.

Day-28 mortality remained between 24% and 28%, and was similar whether the treatment was empiric or targeted, and whether the peritonitis was eventually proven or not.

A delayed initiation of SAT did not impact the prognosis for severely ill patients (SOFA≥7).

The impact of real life treatment strategies for *Candida* peritonitis—A retrospective analysis *Dubler S et al, Mycoses 2017 ;60:440-6*

A retrospective observational single-centre cohort study

Included patients were at least 18 years old, had undergone a laparotomy or interventional drainage placement for source control, and had fungi positive cultures recovered from thereby sterile taken samples.

A total of 137 surgical intensive care unit patients with intra-abdominal invasive Candidiasis were included in the study.

Concomitant polymicrobial intra-abdominal infections were detected in 66 of 137 patients (48.2%)

Fifty six patients did not get any antifungal agent, 29 patients were empirically treated, and 52 patients were specifically treated.

The impact of real life treatment strategies for *Candida* peritonitis—A retrospective analysis *Dubler S et al, Mycoses 2017 ;60:440-6*

OUTCOMES

	No antifungals (n=56)	Empiric antifungal therapy (n=29)	Specific antifungal therapy (n=52)	*P*
30-d mortality	19 (33.9)	14 (48.3)	23 (44.2)	.37
Overall mortality	21 (37.5)	15 (51.7)	32 (61.5)	.043
Following fungaemia	1 (1.8)	1 (3.4)	7 (13.5)	.037
Latency abd. confirmation until fungaemia	7±0	11±0	16.63±18.40	.798
Overall mortality candidaemia	0/2	0/2	4/7 (57.4)	

The impact of real life treatment strategies for *Candida* peritonitis—A retrospective analysis *Dubler S et al, Mycoses 2017 ;60:440-6*

MULTIVARIATE ANALYSIS FOR 30-DAY MORTALITY

	P	Hazard-Ratio (95% confidence interval)
Age (y)	.012	1.038 (1.008-1.069)
Leucocyte count (2/nL)	.020	1.043 (1.007-1.081)
APACHE II score	<.001	1.116 (1.055-1.181)
Acute liver failure	<.001	4.443 (2.328-8.480)
Origin of peritonitis		
Epigastric region	.091	
Small bowel	.144	0.535 (0.231-1.239)
Colon	.057	0.505 (0.250-1.021)
Other	.552	1.264 (0.584-2.739)
Antifungal therapy		
No treatment	.075	
Empirical treatment	.512	0.782 (0.374-1.632)
Specific treatment	.026	0.470 (0.242-0.912)

The impact of real life treatment strategies for *Candida* peritonitis—A retrospective analysis *Dubler S et al, Mycoses 2017 ;60:440-6*

Administered antifungals

	Empiric antifungal therapy (n=29)	Specific antifungal therapy (n=52)	*P*
Primary therapy			
Fluconazole	14 (48.3)	35 (67.3)	<.001
Voriconazole	1 (3.4)	8 (15.4)	.004
Echinocandin	14 (48.3)	9 (17.3)	<.001
Caspofungin	9 (31)	6 (11.5)	<.001
Anidulafungin	5 (17.2)	3 (5.8)	.006
Latency positive result to start of therapy (d)	−2.55±5.94	2.69±2.95	<.001
Secondary therapy	9 (31)	21 (40.4)	<.001
Fluconazole	5 (17.2)	5 (9.6)	.011
Voriconazole	2 (6.9)	7 (13.5)	.019
Echinocandin	2 (6.9)	8 (15.4)	.009
Caspofungin	1 (3.4)	5 (9.6)	.049
Anidulafungin	1 (3.4)	3 (5.8)	.200
Liposomal amphotericin B	0 (0)	1 (1.9)	.440

A Randomized, Placebo-controlled Trial of Preemptive Antifungal Therapy for the Prevention of Invasive Candidiasis Following Gastrointestinal Surgery for Intra-abdominal Infections. *Knitsch W et al, Clin Infect Dis 2015;61:1671-8*

Randomized, double-blind, placebo-controlled trial assessing a preemptive antifungal approach with micafungin (100 mg/d) Patients were included withi they had an expected minir placebo- and 117 micafungin

Baseline Demographic and Clinical Characteristics

Characteristic	Patients, No. (%)[a]		
	Placebo (n = 124)	Micafungin (n = 117)[b]	Total (n = 241)
Sex			
Male	41 (33.1)	50 (42.7)	91 (37.8)
Female	83 (66.9)	67 (57.3)	150 (62.2)
Age, mean (SD), y	63.0 (15.8)	61.6 (14.8)	62.3 (15.3)
Age group			
18–65 y	63 (50.8)	66 (56.4)	129 (53.5)
>65 y	61 (49.2)	51 (43.6)	112 (46.5)
Type of intra-abdominal infection			
CAI	45 (36.3)	41 (35.0)	86 (35.7)
NAI	79 (63.7)	76 (65.0)	155 (64.3)

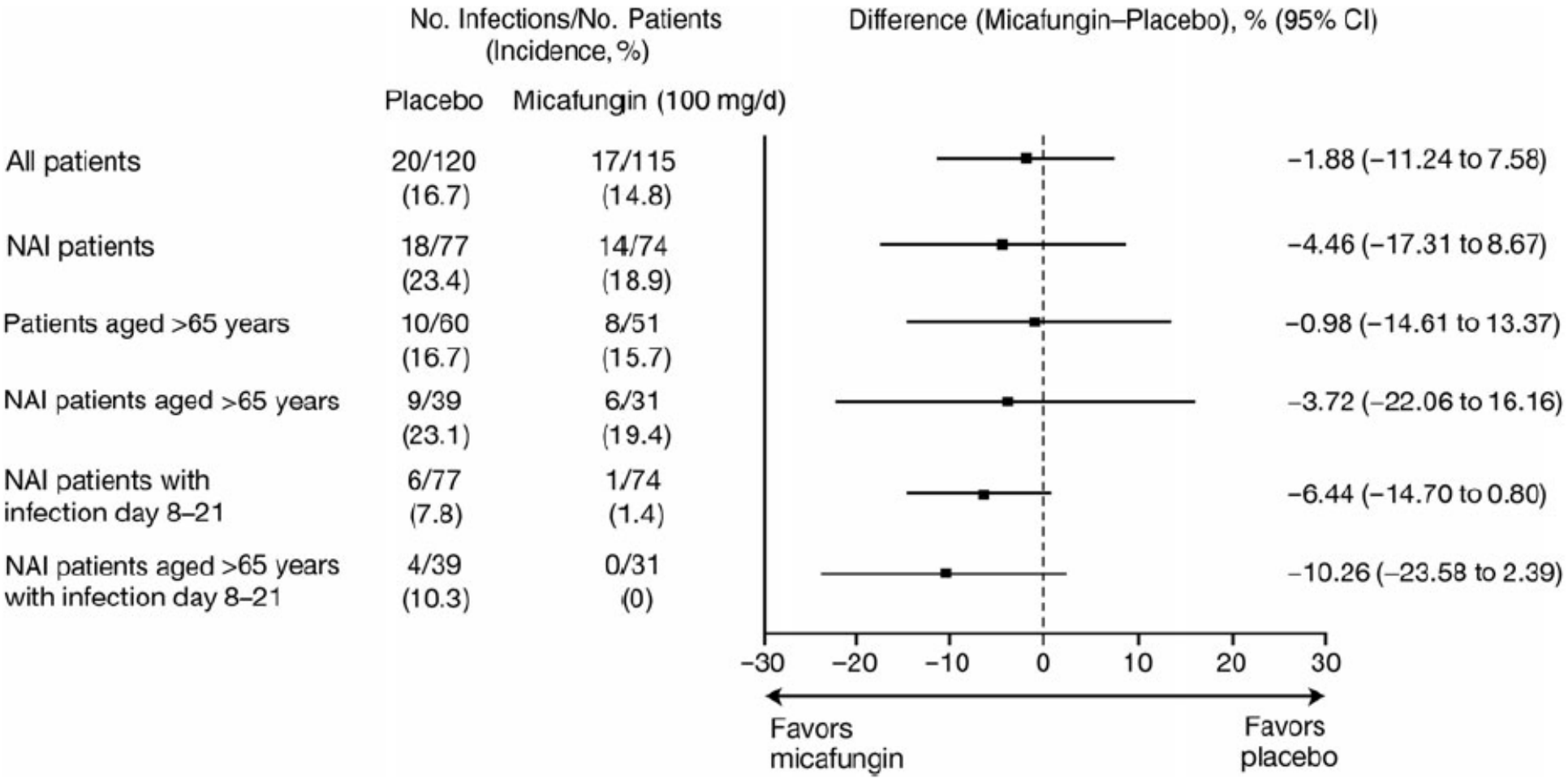
A Randomized, Placebo-controlled Trial of Preemptive Antifungal Therapy for the Prevention of Invasive Candidiasis Following Gastrointestinal Surgery for Intra-abdominal Infections. *Knitsch W et al, Clin Infect Dis 2015;61:1671-8*

Incidence of Invasive Candidiasis in the Full Analysis Set and Per-Protocol Set for All Patients

	Patient With IC/Total Patients, No. (%)		
IC Incidence	Placebo	Micafungin[b]	Treatment Difference (Micafungin – Placebo), % (95% CI)
All patients (FAS)			
IDRB-confirmed IC	11/124 (8.9)	13/117 (11.1)	2.24 (–5.52 to 10.20)
Investigator-confirmed IC[a]	20/121 (16.5)	16/116 (13.8)	–2.74 (–11.92 to 6.56)
Any-confirmed IC[a]	20/120 (16.7)	17/115 (14.8)	–1.88 (–11.24 to 7.58)
All patients (PPS)			
IDRB-confirmed IC	5/88 (5.7)	5/79 (6.3)	0.65 (–7.17 to 8.95)

A Randomized, Placebo-controlled Trial of Preemptive Antifungal Therapy for the Prevention of Invasive Candidiasis Following Gastrointestinal Surgery for Intra-abdominal Infections. *Knitsch W et al, Clin Infect Dis 2015;61:1671-8*

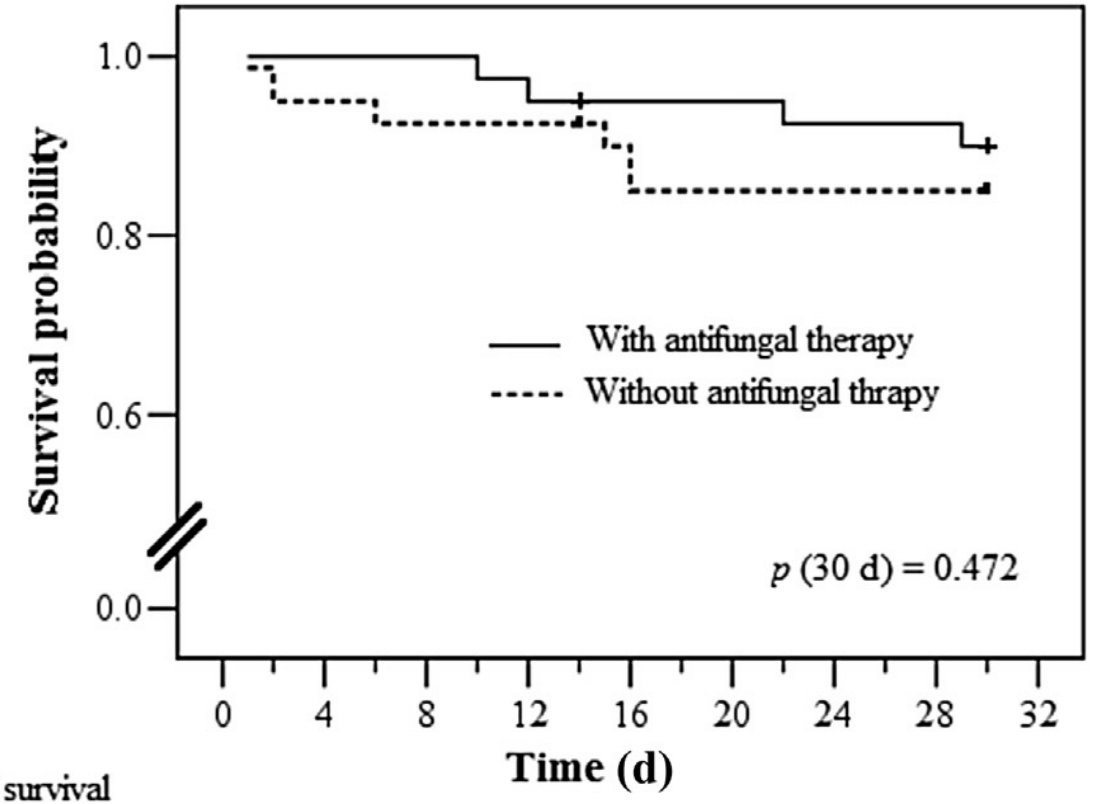
Incidence of confirmed cases of invasive candidiasis by higher-risk subgroups



Antifungal therapy did not improve outcomes including 30-day all-cause mortality in patients suffering community acquired perforated peptic ulcer-associated peritonitis with Candida species isolated from their peritoneal fluid

Wei-Sin Li et al, Journal of Microbiology, Immunology and Infection 2015

a retrospective analysis of the impacts of antifungal therapy on outcomes of patients suffering community-acquired PPU-associated peritonitis with Candida species isolated from their ascites at a medical center in Taiwan. All included patients received source control and antibiotic treatment, with or without additional postoperative antifungal therapy with fluconazole or an echinocandin for at least 3 days. 133 included patients, 76 did not receive and 57 did receive antifungal therapy



Numbers of survival			
With antifungal therapy	40	38	36
Without antifungal thrapy	40	37	34

A systematic review and meta-analysis of diagnostic accuracy of serum 1,3-b-D-glucan for invasive fungal infection: Focus on cutoff levels

He S et al, J Microbiol Immunol Infection 2014

β-D-glucan (BDG) is a cell wall constituent of Candida species and other fungi.

The sensitivity and specificity of serum BDG testing for diagnosing invasive candidiasis have ranged from 57% to 97% and 56% to 93%, respectively

IN THE PRESENT META-ANALYSIS, REGARDING 28 STUDIES, AVERAGE SENSITIVITY AND SPECIFICITY RESULT 78% AND 81%

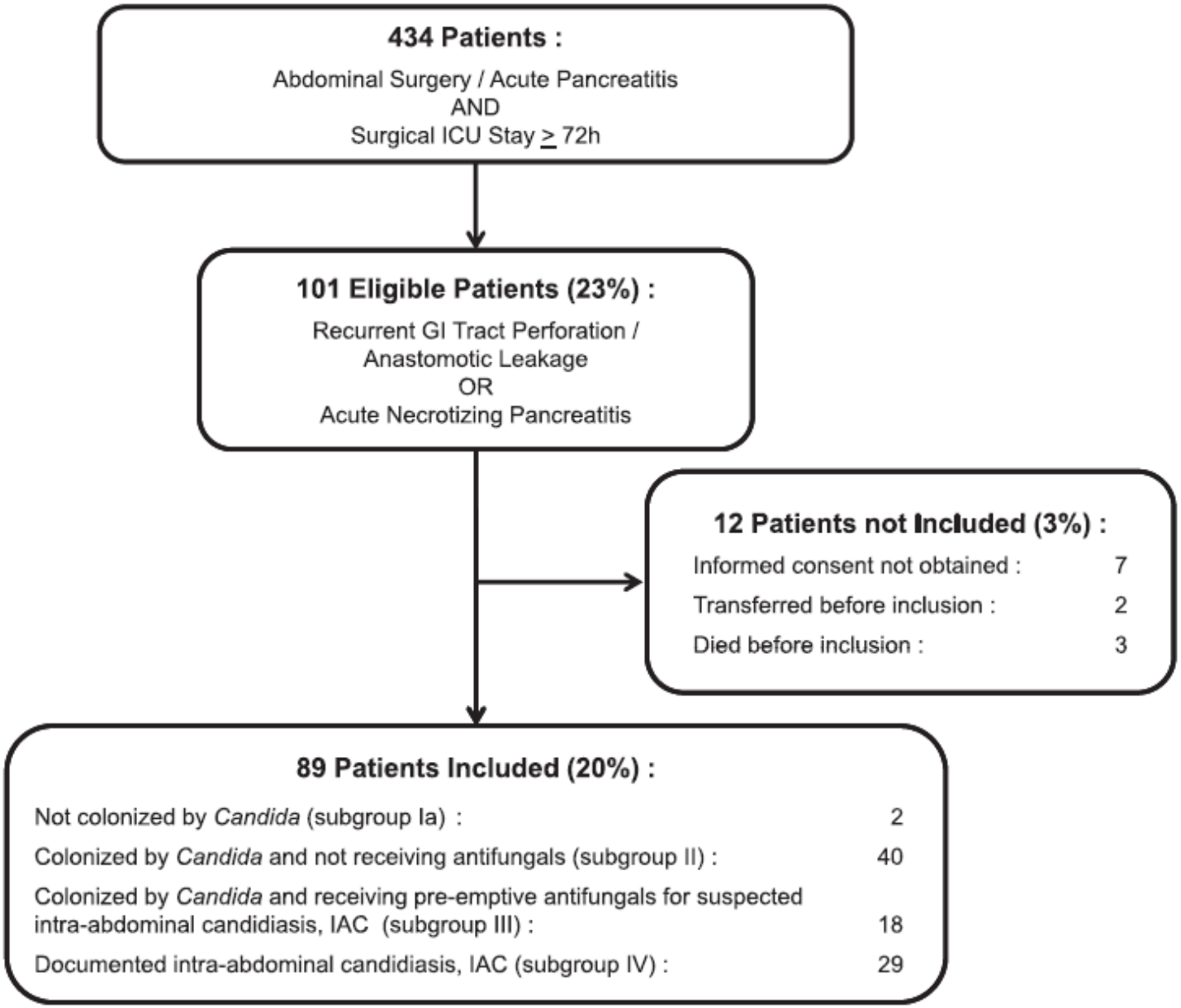
The cutoff value of BDG at 80 pg/mL had the best diagnostic accuracy

Optimal results are achieved if 2 consecutive tests are positive

The major uncertainties for BDG detection are specificity and false-positivity, particularly among high-risk populations

b-Glucan Antigenemia Anticipates Diagnosis of Blood Culture–Negative Intra-abdominal Candidiasis

Tissot F et al, Am J Respir Crit Care Med 2013;188: 1100–1109



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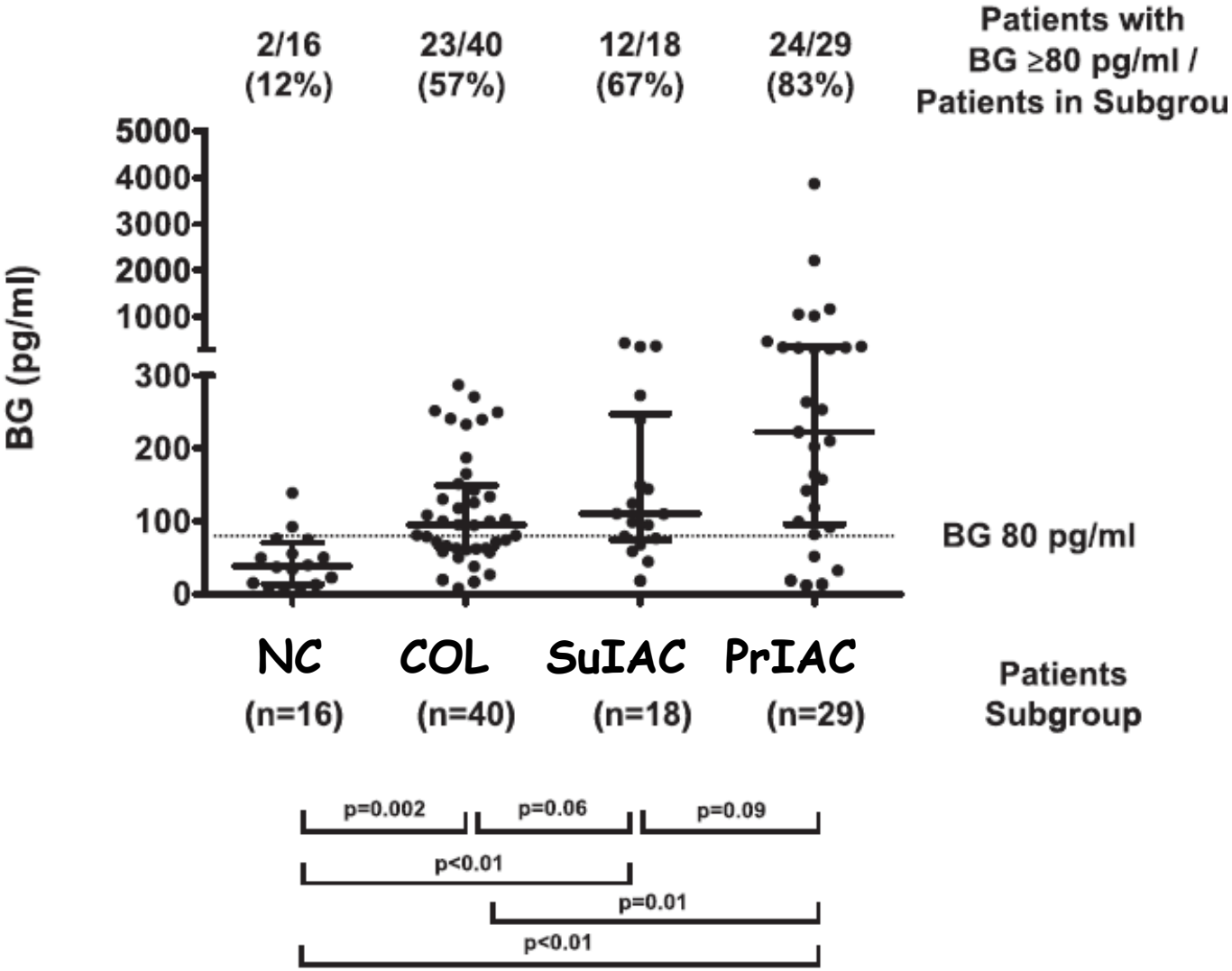


Median BDG

COLONIZED 99 pg/ml (8-440)

IAC 254 pg/ml (46-8557)

Combination of Candida biomarkers in patients receiving empirical antifungal therapy in a Spanish tertiary hospital: a potential role in reducing the duration of treatment

Martinez-Jimenez MC et al, Antimicrob Chemother 2015; 70: 3107–3115

prospective observational study including adults starting empirical antifungal treatment for suspected IC . Patients were stratified according to admission department (ICU or other wards) and final diagnosis (no IC or proven or probable IC).
The Candida albicans germ tube antibody (CAGTA) test and the b-D-glucan (BDG) test were performed on serum samples collected by venepuncture on days 0, 3 and 5 after starting empirical antifungal therapy.

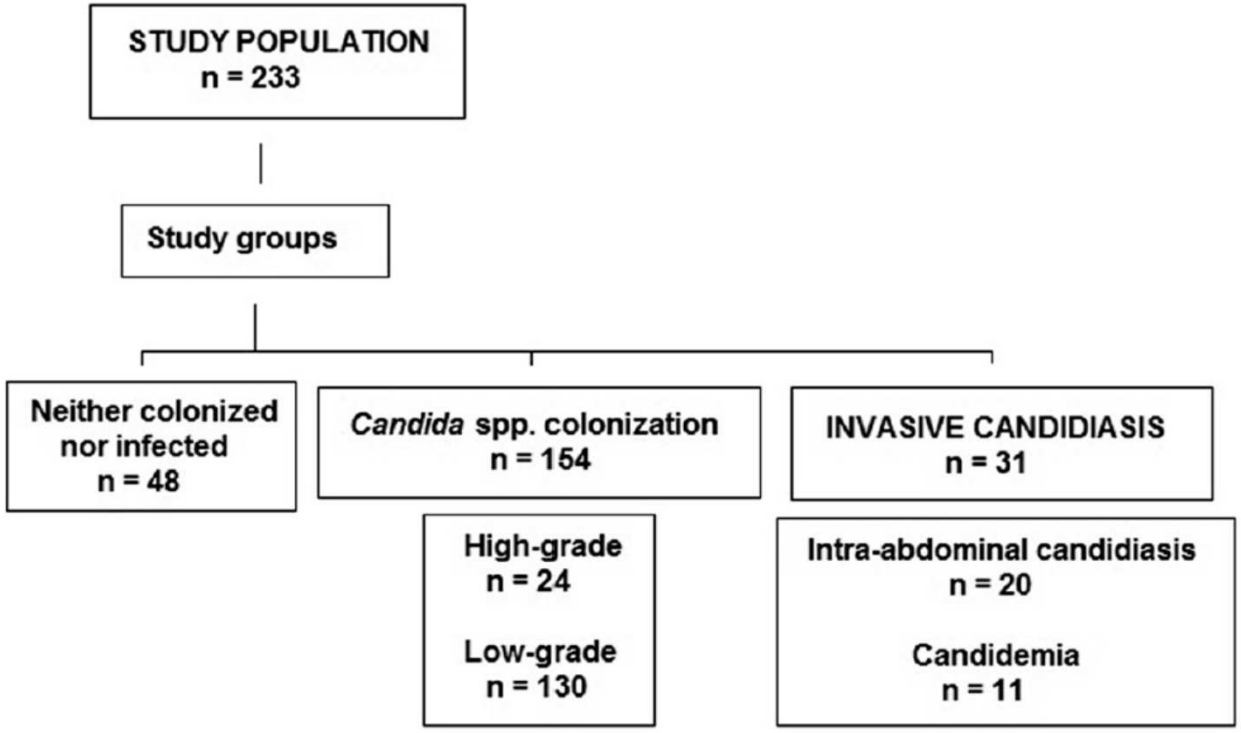
Sixty-three ICU patients and 37 non-ICU patients were included.

Overall, the negative predictive value of the combination of both the CAGTA test and the BDG test was 97% for the entire population.

The best performance was observed in ICU patients (negative predictive value of 100%). Among patients without IC, all biomarkers were negative in 31 patients.

Contribution of Candida biomarkers and DNA detection for the diagnosis of invasive candidiasis in ICU patients with severe abdominal conditions *León C et al, Critical Care 2016; 20:149*

A prospective study of 233 non-neutropenic patients with SAC on ICU admission and expected stay ≥ 7 days. CAGTA (cutoff positivity ≥ 1/160), BDG (≥80, 100 and 200 pg/mL), mannan-Ag (≥60 pg/mL), mannan-Ab (≥10 UA/mL) were measured twice a week, and Candida DNA only in patients treated with systemic antifungals. IC diagnosis required positivities of two biomarkers in a single sample or positivities of any biomarker in two consecutive samples.



Contribution of Candida biomarkers and DNA detection for the diagnosis of invasive candidiasis in ICU patients with severe abdominal conditions *León C et al, Critical Care 2016; 20:149*

Performances of different biomarkers and C-PCR used alone for IC diagnosis

Invasive candidiasis	Sensitivity % (95 % CI)	Specificity % (95 % CI)	NPV % (95 % CI)	PPV % (95 % CI)
BDG ≥ 80 pg/mL	76.7 (57.7–90.1)	57.2 (49.9–64.3)	94.1 (89.1–96.8)	21.7 (17.7–26.4)
BDG ≥ 100 pg/mL	70.0 (50.6–85.3)	61.5 (54.3–68.4)	93.0 (88.4–95.9)	21.9 (17.3–27.3)
BDG ≥ 200 pg/mL	60.0 (40.6–77.3)	79.4 (73.1–84.8)	92.9 (89.4–95.4)	30.5 (22.7–39.6)
CAGTA positive	53.3 (34.3–71.7)	64.3 (57.2–71.0)	90.1 (86.0–93.2)	18.4 (13.3–24.8)
Mannan-Ag positive	43.3 (25.5–62.6)	67.3 (60.3–73.8)	88.7 (85.0–91.6)	16.7 (11.3–24.0)
Mannan-Ab positive	25.8 (11.9–44.6)	89.0 (83.8–93.0)	88.6 (86.2–90.6)	26.7 (15.1– 42.6)
C-PCR positive	84.0 (63.9–95.5)	32.9 (23.1–44.0)	87.5 (73.1–94.8)	26.9 (22.7–31.6)

Contribution of Candida biomarkers and DNA detection for the diagnosis of invasive candidiasis in ICU patients with severe abdominal conditions *León C et al, Critical Care 2016; 20:149*

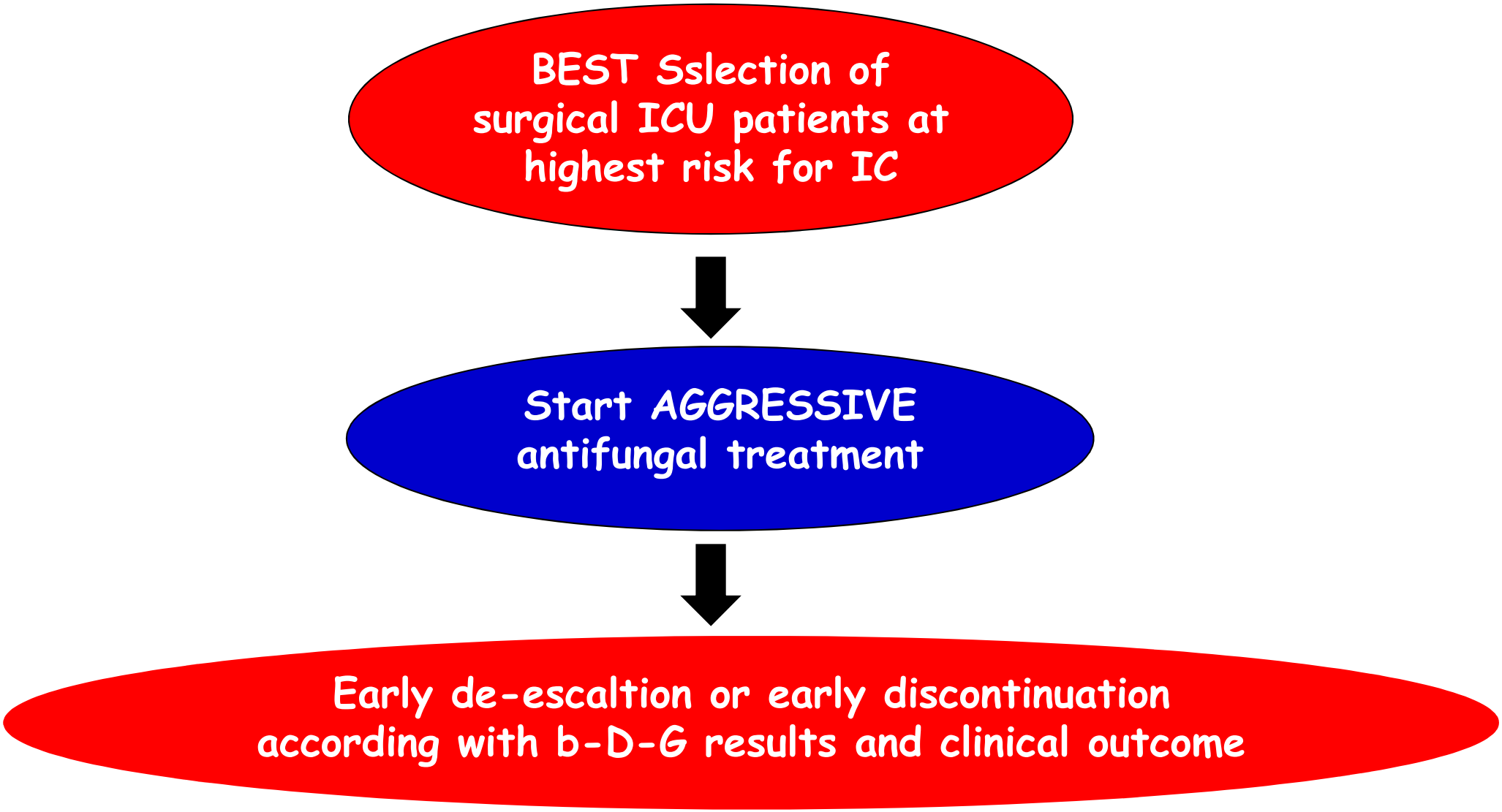
Performances of different biomarkers combinations for IC diagnosis

Invasive candidiasis		Sensitivity % (95 % CI)	Specificity % (95 % CI)	NPV % (95 % CI)	PPV % (95 % CI)
BDG ≥80 pg/mL	CAGTA	90.3 (74.2–98.0)	42.1 (35.2–49.2)	96.6 (90.5–98.8)	19.3 (16.9–22.0)
	Mannan-Ag	80.6 (62.5–92.5)	44.1 (37.1–51.2)	93.7 (87.7–96.9)	18.1 (15.2–21.5)
	Mannan-Ab	74.2 (42.9–57.1)	50.0 (42.9–57.1)	92.7 (87.2–95.9)	18.5 (15.1–22.6)
	C-PCR	76.0 (54.9–90.6)	40.0 (29.5–51.2)	85.0 (72.9–92.3)	27.1 (22.0–33.0)
BDG ≥100 pg/mL	CAGTA	83.9 (66.3–94.5)	44.1 (37.1–51.2)	94.7 (88.7–97.6)	18.7 (15.9–21.9)
	Mannan-Ag	74.2 (55.4–88.1)	46.5 (39.5–53.7)	92.2 (86.4–95.6)	17.6 (14.3–21.4)
	Mannan-Ab	67.7 (48.6–83.3)	53.5 (46.3–60.5)	91.5 (86.5–94.8)	18.3 (14.4–22.9)

the combination of BDG and CAGTA positivities in a single determination or at least one of the two biomarkers positive in two consecutive samples, allowed discriminating between IC and the groups of low-grade and high-grade Candida colonization as well as neither colonized nor infected. Other tests including PCR Candida DNA detection and serum levels of mannan-Ag and mannan-Ab alone or combined did not improve the diagnostic yield.

CAGTA positive	Mannan-Ag	67.7 (48.6–83.3)	51.0 (43.9–58.1)	91.2 (85.9–94.6)	17.5 (13.8–21.9)
	Mannan-Ab	64.5 (45.4–80.8)	57.9 (50.8–64.8)	91.4 (86.7–94.5)	19.0 (14.8–24.2)
	C-PCR	56.0 (34.9–75.6)	55.3 (44.1–66.1)	81.0 (72.5–87.4)	26.9 (19.5–35.9)
C-PCR positive	Mannan-Ag	60.0 (38.7–78.9)	63.5 (52.4–73.7)	84.4 (76.5–90.0)	32.6 (24.0–42.5)
	Mannan-Ab	54.8 (36.0–72.7)	78.7 (72.4–84.1)	91.9 (88.4–94.4)	28.3 (20.7–37.5)
Mannan-Ag positive	Mannan-Ab	54.8 (36.0–72.7)	59.9 (52.8–66.7)	89.6 (85.2–92.8)	17.3 (12.8–23.1)

Antifungal stewardship – a proposal



Association between source control and mortality in 258 patients with intra-abdominal candidiasis: a retrospective multi-centric analysis comparing intensive care versus surgical wards in Spain. *Lagunes L et al Eur J Clin Microbiol Infect Dis 2017; 36:95–104*

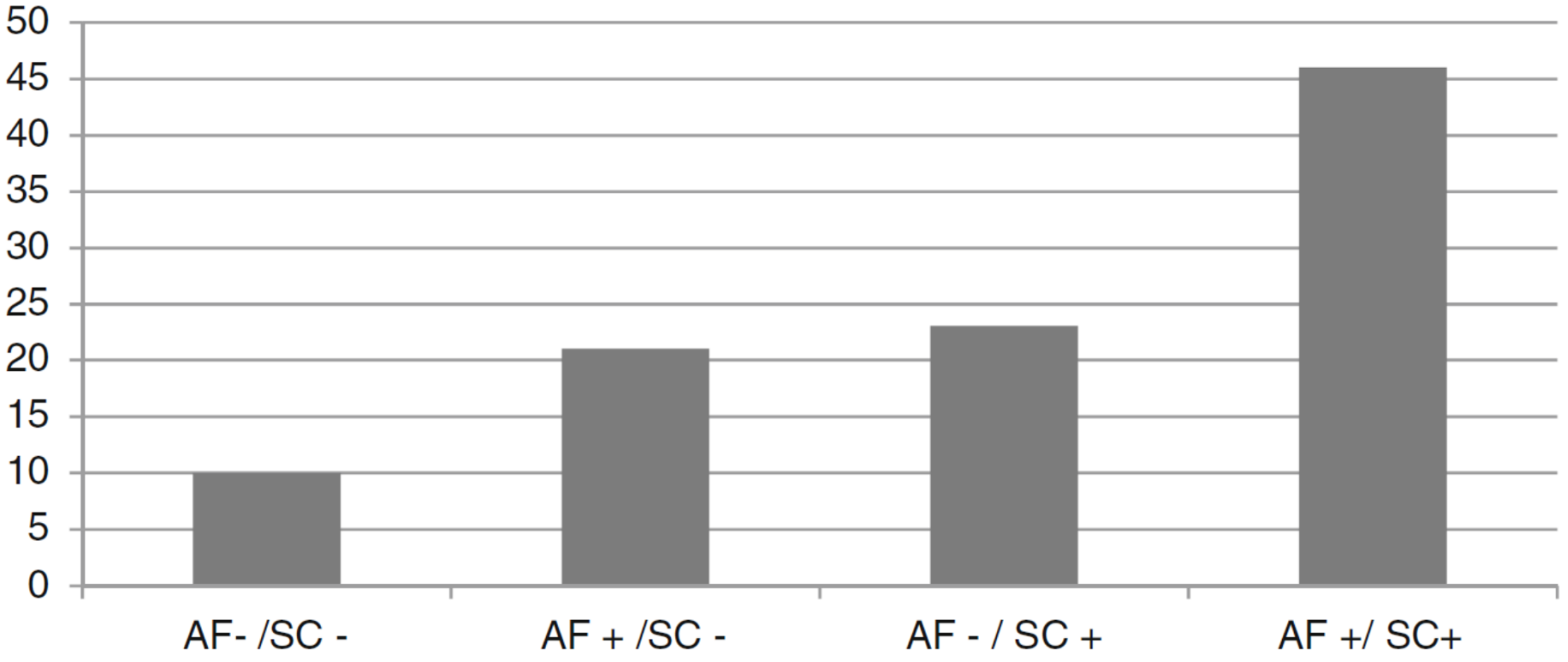
A retrospective, multicenter, cohort study, performed at surgical wards and intensive care units of three University Hospitals in Spain between 2010 and 2014, with the aim of improving understanding of the interaction between source control, early antifungal therapy, and use of vasoactives in patients with intra-abdominal candidiasis. 258 pts identified.

Independent risk factors for 30-day mortality in ICU and surgical ward patients

Variable	ICU		Regular wards	
	OR 95 % CI	*P* value	OR 95 % CI	*P* value
Age >65 years			2.23 (0.91–5.48)	0.078
Peritonitis			2.46 (0.99–6.13)	0.052
APACHE >15	10.18 (1.86–55.7)	0.007		
Vasopressors	4.80 (0.67–34.31)	0.118	10.63 (3.8–29.72)	<0.001
No treatment	5.94 (1.35–26.11)	0.018		
Inadequate source control	13.78 (2.60–72.9)	0.002	6.53 (2.56–16.61)	<0.001
Inadequate antifungal			2.38 (0.91–6.21)	0.076

Association between source control and mortality in 258 patients with intra-abdominal candidiasis: a retrospective multi-centric analysis comparing intensive care versus surgical wards in Spain. *Lagunes L et al Eur J Clin Microbiol Infect Dis 2017; 36:95–104*

SURVIVALS



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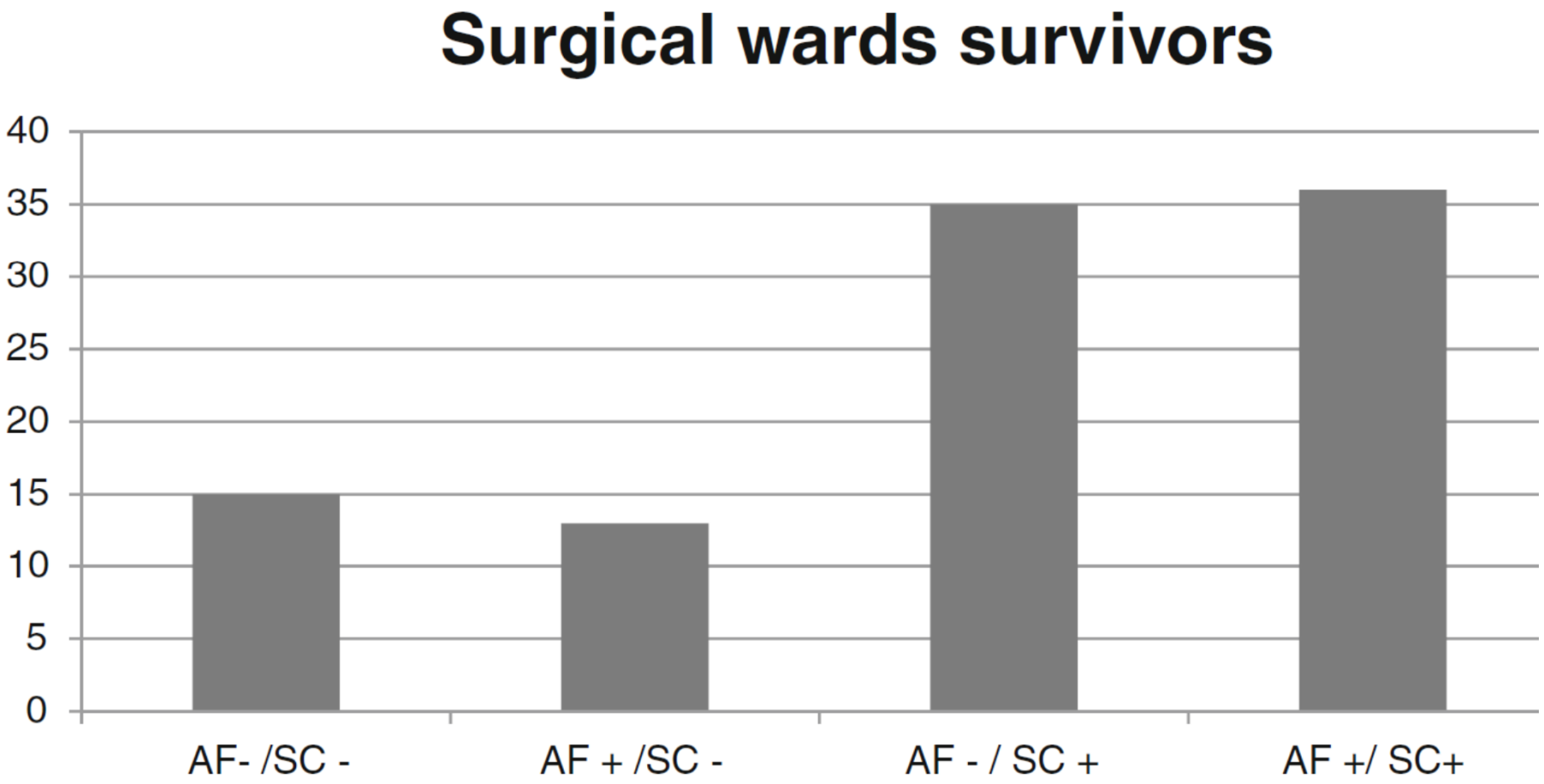
SURVIVALS



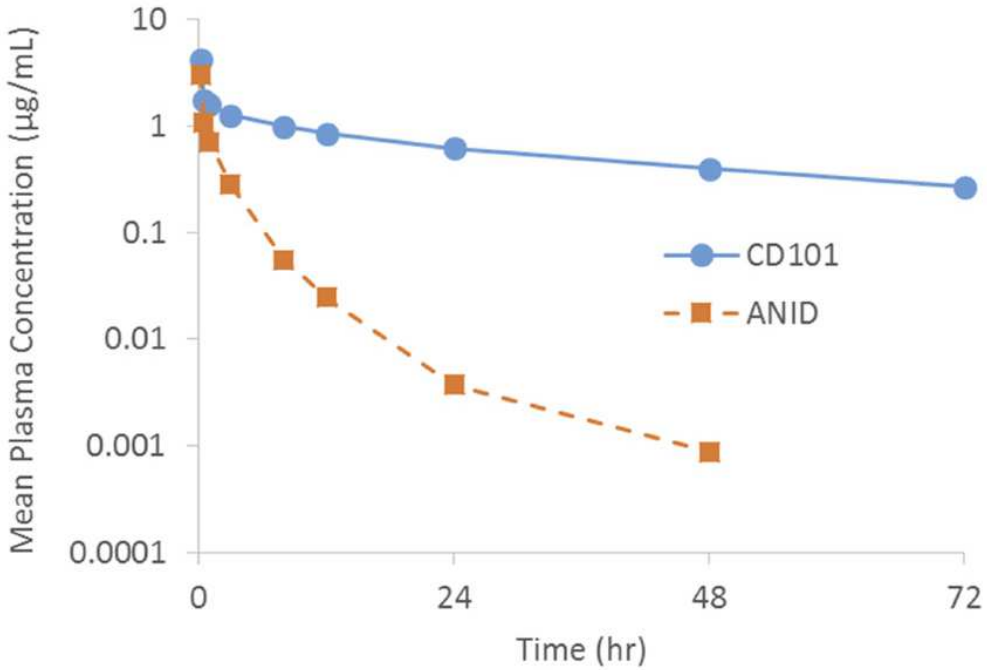
Unraveling Drug Penetration of Echinocandin Antifungals at the Site of Infection in an Intra-abdominal Abscess Model *Zhao Y et al Antimicrob Agents Chemother 2017; 61:e01009-17.*

Using matrix-assisted desorption ionization mass spectrometry imaging technology, the spatial and quantitative distribution in tissue lesions for two echinocandin drugs, micafungin and CD101, was investigated in a clinically relevant IAC mouse model.

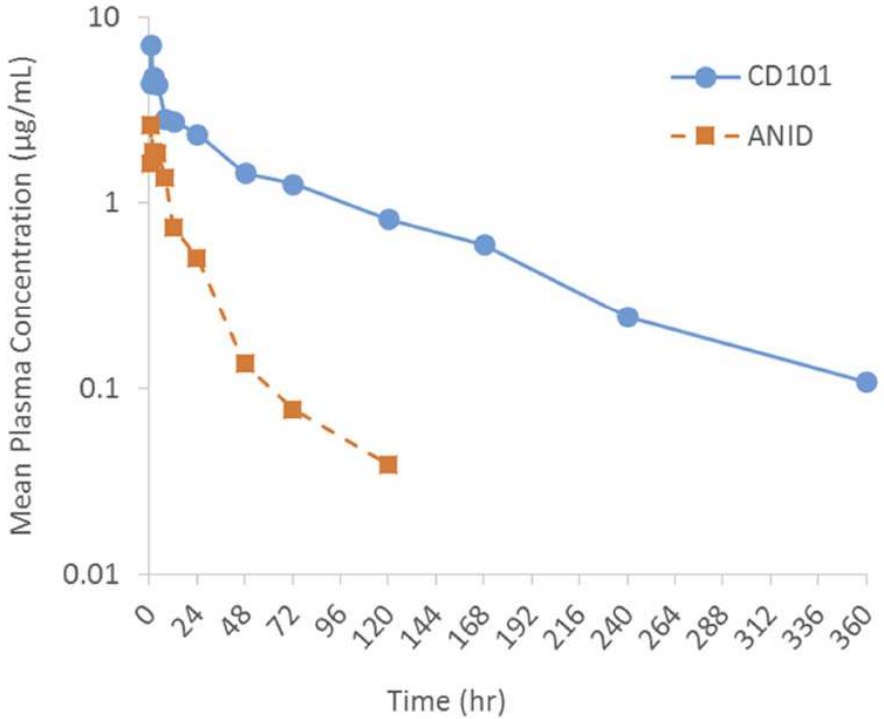
Pharmacokinetics of the Novel Echinocandin CD101 in Multiple Animal

Species Ong V et al , Antimicrob Agents Chemother 2017; 61:e01626-16.

(c) Cynomolgus Monkey (n=3/group)



(d) Chimpanzee (n=2/group)

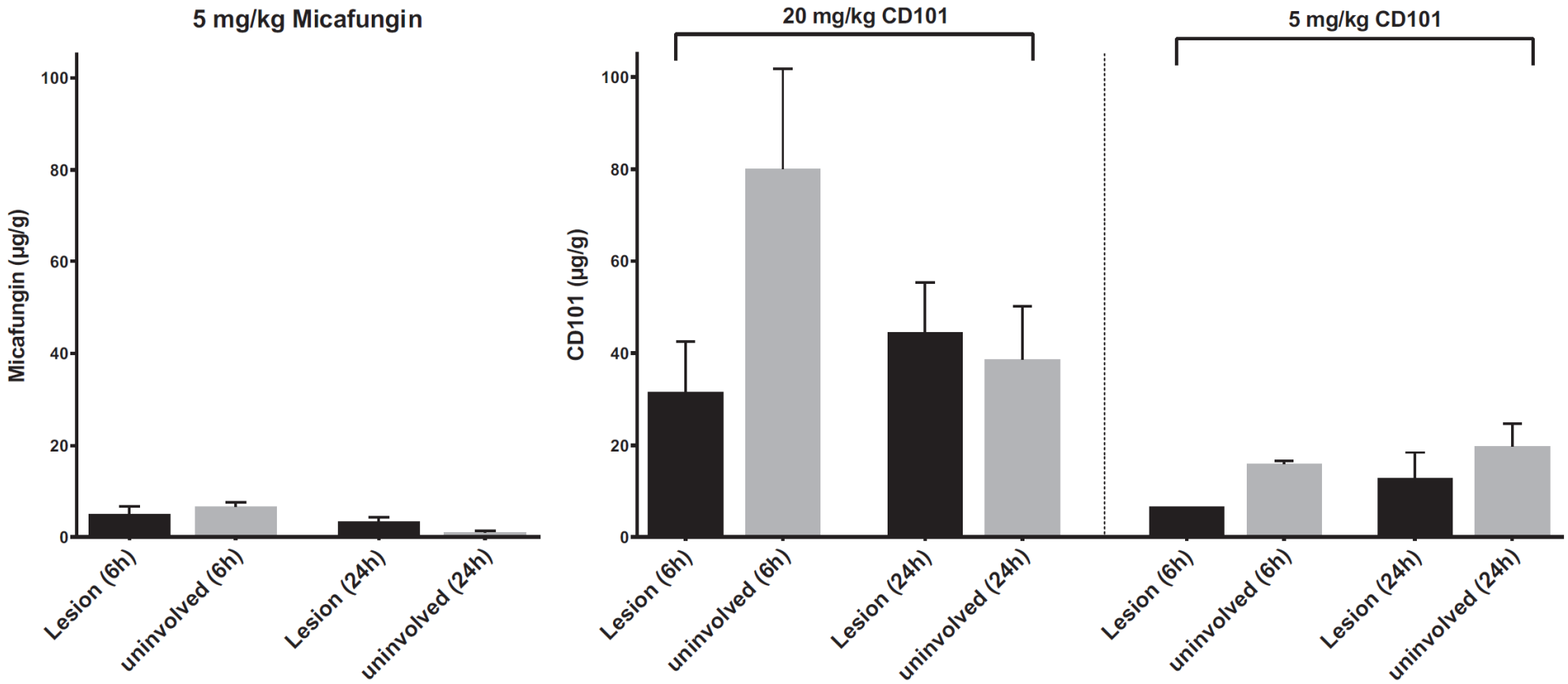


CD101's concentration-dependent pattern of fungicidal activity in combination with its slow clearance from the body, has important implications for dose regimen selection and front-loading drug exposure (i.e., maximizing drug effect early in the course of therapy to increase the rate and extent of pathogen killing, reduce and prevent resistance, and ultimately improve clinical outcomes)

Unraveling Drug Penetration of Echinocandin Antifungals at the Site of Infection in an Intra-abdominal Abscess Model *Zhao Y et al Antimicrob Agents Chemother 2017; 61:e01009-17.*

Using matrix-assisted desorption ionization mass spectrometry imaging technology, the spatial and quantitative distribution in tissue lesions for two echinocandin drugs, micafungin and CD101, was investigated in a clinically relevant IAC mouse model.

Quantification of drug exposure in liver lesions and surrounding tissues



Unraveling Drug Penetration of Echinocandin Antifungals at the Site of Infection in an Intra-abdominal Abscess Model

Zhao Y et al Antimicrob Agents Chemother 2017; 61:e01009-17.

Drug distribution in infected liver tissues after single doses of micafungin and CD101