Ferrara, 27 novembre 2015

Infezioni in chirurgia: nuove acquisizioni per nuove indicazioni

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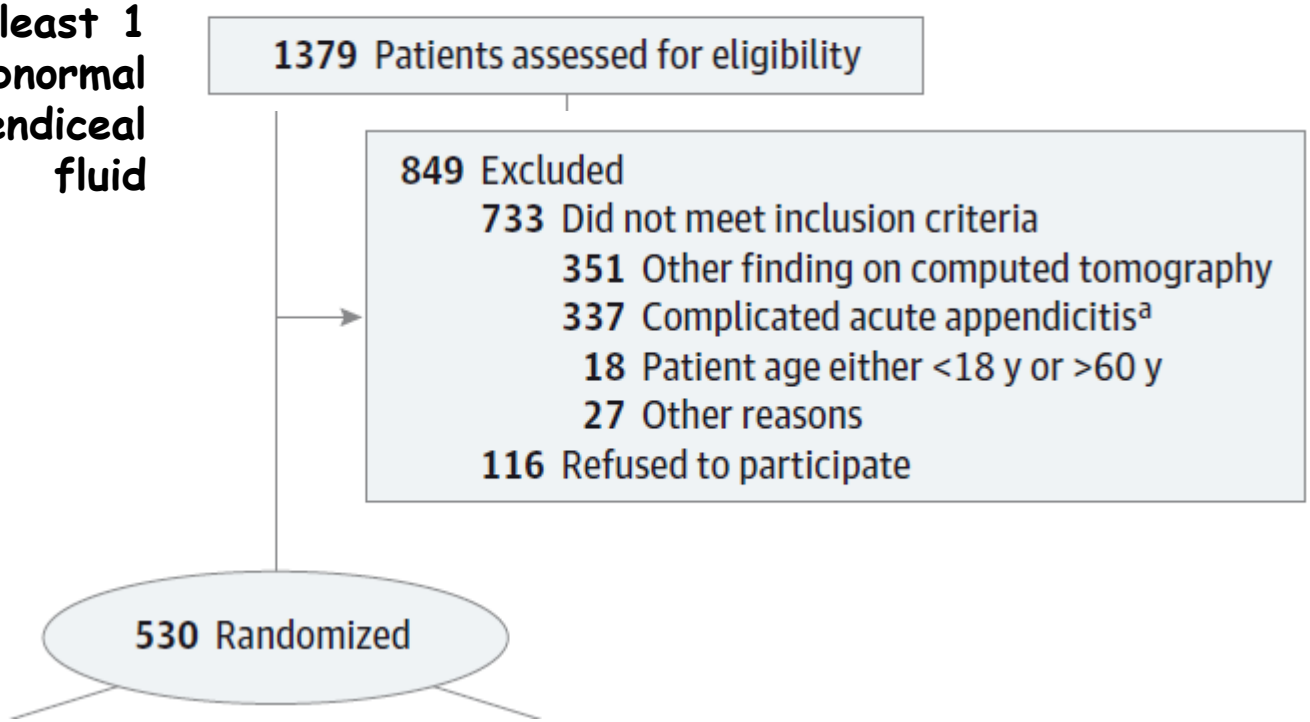
- INDICATION TO TREATMENT
- DURATION OF TREATMENT
- THE CONUNDRUM OF INTRA-ABDOMINAL CANDIDIASIS
- THE ANTIBIOTIC CHOICE IN THE ERA OF ANTIBIOTIC CRISIS
- PUTATIVE INDICATIONS OF NEW ANTIBIOTICS IN IAI

Antibiotic therapy vs Appendectomy for treatment of uncomplicated acute appendicitis. The APPAC Randomized Clinical Trial.

Salminen P et al, JAMA 2015; 313:2340-2348

Acute appendicitis was considered present when the appendiceal diameter exceeded 6 mm with wall thickening and at least 1 of the following was present: abnormal contrast enhancement of the appendiceal wall, inflammatory edema, or fluid collections around the appendix.



Patients randomized to antibiotic therapy received intravenous ertapenem (1 g/d) for 3 days followed by 7 days of oral levofloxacin (500mg once daily) and metronidazole (500mg 3 times per day).

Patients randomized to the surgical treatment group were assigned to undergo standard open appendectomy

The primary end point for the surgical intervention was the successful completion of an appendectomy. The primary end point for antibiotic-treated patients was discharge from the hospital without the need for surgery and no recurrent appendicitis during a 1-year follow-up.

Antibiotic therapy vs Appendectomy for treatment of uncomplicated acute appendicitis. The APPAC Randomized Clinical Trial.

Salminen P et al, JAMA 2015; 313:2340-2348

Of the 273 patients randomized to the surgical group, all but 1 underwent successful appendectomy, resulting in a success rate of 99.6% (95%CI, 98.0%-100.0%).

Of the 256 patients available for 1-year follow-up in the antibiotic group, 186 (72.7%; 95%CI, 66.8%to 78.0%) did not require appendectomy. Seventy patients (27.3%; 95%CI, 22.0% to 33.2%) in the antibiotic group underwent surgical intervention within 1 year of initial presentation for appendicitis

Major Randomized Clinical Trials Comparing Antibiotic Therapy With Appendectomy in Patients With Acute Appendicitis

Source	Inclusion Criteria	Age Group, y	No. of Patients	Antibiotic Used for Nonsurgical Patients	Appendectomy in Patients Treated With Antibiotics[a]	Limitations
Styrud et al,[8] 2006	Clinical diagnosis and CRP >10 mg/L	18-50	Surgery: 124 Antibiotic: 128	IV: cefotaxime plus tinidazole Oral: ofloxacin plus tinidazole	31/128 (24)	Female patients excluded, primary end point unclear
Hansson et al,[7] 2009	Clinical diagnosis	>18	Surgery: 167 Antibiotic: 202	IV: cefotaxime plus metronidazole Oral: ciprofloxacin plus metronidazole	96/202 (48)	52.5% of patients in the antibiotic group crossed over to the surgery group
Vons et al,[9] 2011	CT imaging	>18	Surgery: 119 Antibiotic: 120	IV: amoxicillin plus clavulanic acid Oral: amoxicillin plus clavulanic acid	44/120 (37)	Included patients with complicated acute appendicitis (appendicolith), suboptimal antibiotic for intra-abdominal infections

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Duration of antibiotic treatment after appendicectomy for acute complicated appendicitis

van Rossem CC et al, BJS 2014; 101: 715–719

Observational cohort study of all adult patients who had an appendicectomy between January 2004 and December 2010 at either one of two hospitals in the same region. At location A, the protocol included 3 days of postoperative antibiotic treatment, whereas at location B it specified 5 days. The primary outcome was the development of postoperative infections as either superficial wound infection or deep intra-abdominal infections.
A total of 1143 patients with acute appendicitis underwent appendicectomy, of whom 267 (23.4 %) had complicated appendicitis

		All infectious complications	
	Prevalence in first group (%)	Odds ratio	*P*
Antibiotic treatment (3 *versus* 5 days)*	50·6	1·70 (0·72, 4·01)	0·223
Sex (M *versus* F)	53·2	1·03 (0·46, 2·32)	0·943
Age (> 50 *versus* ≤ 50 years)	39·7	0·94 (0·41, 2·17)	0·892
Operator (resident *versus* surgeon)	52·4	1·07 (0·47, 2·40)	0·879
Location (A *versus* B)	47·2	1·34 (0·60, 3·03)	0·475
Approach (laparoscopic *versus* open)·	32·6	1·90 (0·84, 4·30)	0·125

In multivariable logistic regression analysis, ATB treatment (3 *vs* 5 days) corrected for location and approach yielded an OR of 1.56 (95% CI 0.53 to 4.6; *P* =0.215) for all infectious complications

Duration of antibiotic treatment after appendicectomy for acute complicated appendicitis

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Observational cohort study of all adult patients who had an appendicectomy between January 2004 and December 2010 at either one of two hospitals in the same region. At location A, the protocol included 3 days of postoperative antibiotic treatment, whereas at location B it specified 5 days. The primary outcome was the development of postoperative infections as either superficial wound infection or deep intra-abdominal infections.
A total of **1143 patients** with acute appendicitis underwent appendicectomy, of whom 267 (23.4 %) had complicated appendicitis

		Intra-abdominal abscess	
	Prevalence in first group (%)	Odds ratio	*P*
Antibiotic treatment (3 *versus* 5 days	50·6	1·77 (0·68, 4·58)	0·242
Sex (M *versus* F)	53·2	1·19 (0·48, 2·30)	0·705
Age (> 50 *versus* ≤ 50 years)	39·7	1·08 (0·43, 2·69)	0·876
Operator (resident *versus* surgeon)	52·4	1·23 (0·50, 3·02)	0·653
Location (A *versus* B)	47·2	1·91 (0·77, 4·78)	0·165
Approach (laparoscopic *versus* oper	32·6	2·46 (1·00, 6·04)	0·049

In multivariable logistic regression analysis, ATB treatment (3 *vs* 5 days) corrected for location and approach yielded an OR of 1.13 (0.33 to 3.85; *P* =0. 844) for intra-abdominal abscess.

Trial of Short-Course Antimicrobial Therapy for Intra-abdominal Infection

Sawyer RG et al N Engl J Med 2015; 372:1996-2005

518 patients with complicated intraabdominal infection and adequate source control ewere randomly assigned to receive antibiotics until 2 days after the resolution of fever, leukocytosis, and ileus, with a maximum of 10 days of therapy (control group), or to receive a fixed course of antibiotics (experimental group) for 4±1 calendar days. The primary outcome was a composite of surgical-site infection, recurrent intraabdominal infection, or death within 30 days after the index source-control procedure, according to treatment group. Secondary outcomes included the duration of therapy and rates of subsequent infections.

Characteristics of index infection		
APACHE II score‡	9.9±0.4	10.3±0.4
Maximum white-cell count — per mm^3	15,600±0.4	17,100±0.7
Maximum body temperature — °C	37.8±0.1	37.7±0.1
Organ of origin — no. (%)		
Colon or rectum	80 (30.8)	97 (37.6)
Appendix	34 (13.1)	39 (15.1)
Small bowel	31 (11.9)	42 (16.3)
Source-control procedure — no. (%)		
Percutaneous drainage	86 (33.1)	86 (33.3)
Resection and anastomosis or closure	69 (26.5)	64 (24.8)
Surgical drainage only	55 (21.2)	54 (20.9)
Resection and proximal diversion	27 (10.4)	37 (14.3)
Simple closure	20 (7.7)	12 (4.7)
Surgical drainage and diversion	3 (1.2)	4 (1.6)

Trial of Short-Course Antimicrobial Therapy for Intra-abdominal Infection

Sawyer RG et al N Engl J Med 2015; 372:1996-2005

Duration of outcome — days	Control Group (N=260)	Experimental Group (N=257)	P Value
Antimicrobial therapy for index infection			<0.001
Median	8	4	
Interquartile range	5–10	4–5	
Antimicrobial-free days at 30 days			<0.001
Median	21	25	
Interquartile range	18–25	21–26	
Hospitalization after index procedure			0.48
Median	7	7	
Interquartile range	4–11	4–11	
Hospital-free days at 30 days			0.22
Median	23	22	
Interquartile range	18–26	16–26	

Trial of Short-Course Antimicrobial Therapy for Intra-abdominal Infection

Sawyer RG et al N Engl J Med 2015; 372:1996-2005

Variable	Control Group (N=260)	Experimental Group (N=257)	P Value
Primary outcome: surgical-site infection, recurrent intraabdominal infection, or death — no. (%)	58 (22.3)	56 (21.8)	0.92
Surgical-site infection	23 (8.8)	17 (6.6)	0.43
Recurrent intraabdominal infection	36 (13.8)	40 (15.6)	0.67
Death	2 (0.8)	3 (1.2)	0.99
Time to event — no. of days after index source-control procedure			
Diagnosis of surgical-site infection	15.1±0.6	8.8±0.4	<0.001
Diagnosis of recurrent intraabdominal infection	15.1±0.5	10.8±0.4	<0.001
Death	19.0±1.0	18.5±0.5	0.66

Protocol violation **18%** **27%**

median of 11 days of antimicrobials

A procalcitonin based algorithm to guide antibiotic therapy in secondary peritonitis following emergency surgery: A prospective study with propensity score matching analysis. *TS, et al. PLoS One 2014;9:e90539.*

patients diagnosed at the emergency department with secondary peritonitis and underwent emergency surgery were enrolled. PCT concentrations were obtained preoperatively, on post-operative days 1, 3, 5, and 7, and on subsequent days if needed. Antibiotics were discontinued if PCT was <1.0 ng/mL or decreased by 80% versus day 1, with resolution of clinical signs.

	PCT group	*Control*	*p*
median duration of antibiotics (days)	**3.4**	**6.1**	**< 0.001**

the PCT-based algorithm was substantially associated with a 87% reduction in hazard of antibiotic exposure within 7 d (HR) 0.13, 95% CI 0.07–0.21, and a 68% reduction in hazard after 7 d (adjusted HR 0.32, 95% CI 0.11-0.99)

Procalcitonin-guided therapy may reduce length of antibiotic treatment in intensive care unit patients with secondary peritonitis: A multicenter retrospective study. *Maseda E, et al. J Crit Care 2015;30:537–542*

A total of 121 patients (52 PCT-guided, 69 non-PCT-guided) were enrolled

	PCT	*control*	*p*
Median length of intra-SICU (days)	5	5	NS
Median LOS	20	17	NS
In-H Mortality (%)	9.6	13	NS
28 day mortality	19.2	29	NS
ATB duration /days)	5.1	10.2	<.001

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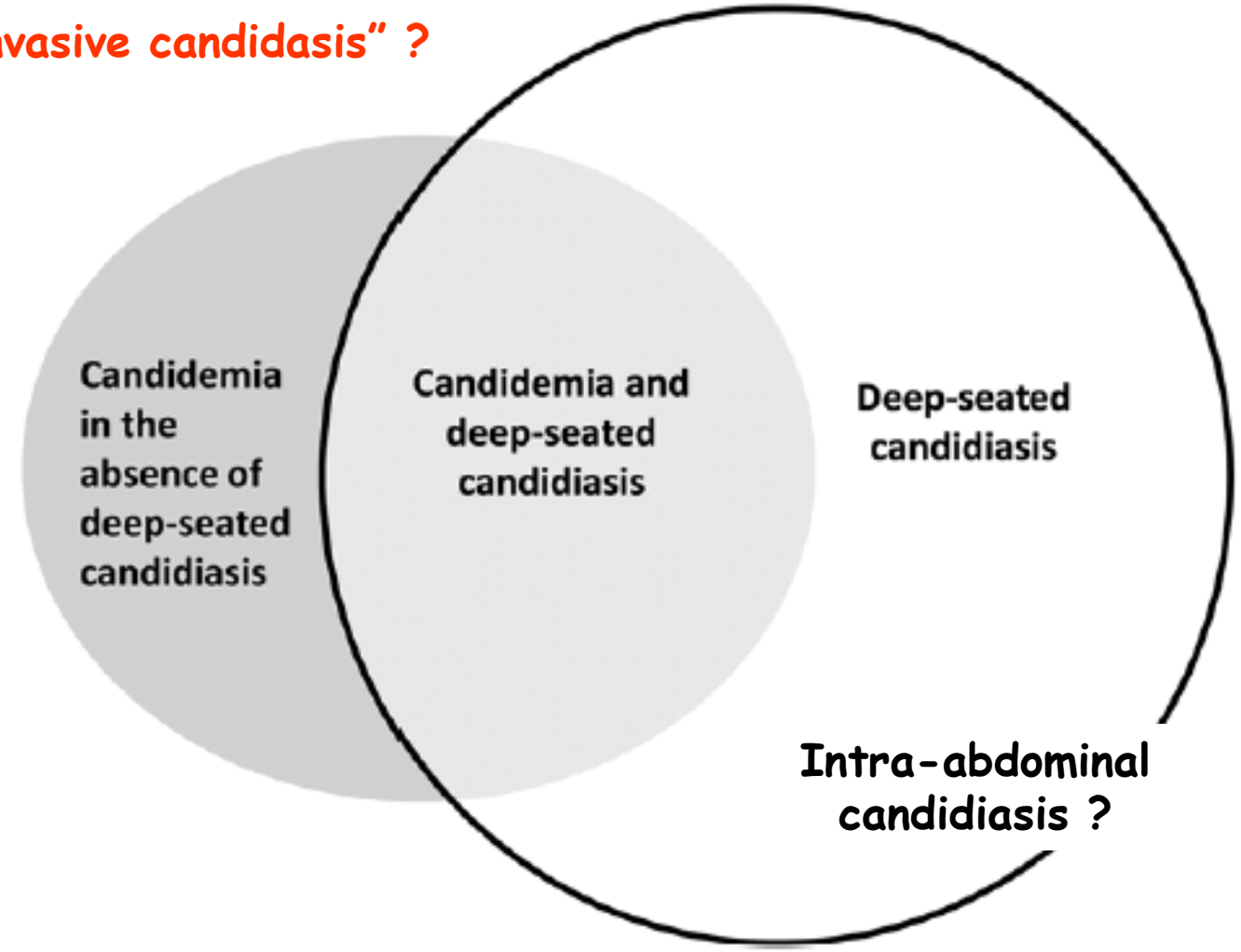
Finding the "missing 50%" of invasive candidiasis: How non-culture diagnostics will improve understanding of disease spectrum and transform patient care.

Clancy CJ, Nguyen MH Clin Infect Dis 2013 Jan 11

What does it mean "invasive candidasis" ?



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)

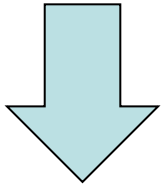
	Univariate analysis		Multivariate analysis	
RISK FACTORS	OR (95% CI)	p value	OR (95% CI)	p value
Case group (Candida +)	2.4 (1.2-4.6)	.01	3.0 (1.3-6.7)	.009
Upper GI tract site	2.1 (1.1-4.1)	.02	4.9 (1.6-14.8)	.005
Empirical antifungal Rx	1.9 (0.9-3.9)	.07	-	
Inappropriate ATB therapy	2.2 (1.1-4.3)	.02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

A multicentre study of antifungal strategies and outcome of Candida spp. peritonitis in intensive-care units. *Montravers P et al – Clin Microbiol Infect 2011; 17*

271 adult intensive-care unit (ICU) patients with proven invasive Candida infection who received systemic antifungal therapy.

93 had Candida peritonitis, including 73 nosocomial peritonitis.



Mortality rate peritonitis: 38%

Impact of Therapeutic Strategies on the Prognosis of Candidemia in the ICU

Puig-Asensio M et al, Critical Care Med 2014

Prospective, observational, multicenter population- based study performed in medical and surgical ICUs in 29 hospitals distributed throughout five metropolitan areas of Spain.
752 cases of candidemia were detected: among these, 168 (22.3%) occurred in ICU patients

Risk factors for candidemia		
Previous antibiotic therapy	164	(97.6)
Central venous catheter	162	(97.6)
Renal replacement therapyc	39	(23.2)
Previous surgery (3 mo)	111	(66.1)
→ Abdominal surgery	60/111	(54.1)
Parenteral nutrition	106	(63.1)
Previous *Candida* colonization	95	(56.5)
Previous hospitalization (3 mo)	67	39.9)
Neutropenia at candidemia onset	8	(4.8)
Previous corticosteroids (1 mo)	65	(38.7)
Recent antifungal exposure (< 1 mo)	54	(32.1)
Azoles	36/54	(21.4)
Echinocandins	25/54	(14.9)

Can yeast isolation be predicted in complicated secondary non-postoperative intra-abdominal infections?

Dupont H et al. Critical Care 2015; 19:60

All patients with a CNPIAI undergoing emergency surgery over a three-year period were included in the retrospective cohort (RC, n = 290). Patients with a yeast-positive peritoneal fluid culture (YP) were compared with patients with a yeast-negative culture (YN). Multivariate logistic regression was used to identify factors independently associated with yeast isolation and a predictive score was built. The score's performance was then established in the prospective cohort (PC, n = 152) over an 18-month period. Outcome of the whole cohort was evaluated and independent risks factors of mortality searched

Lower gastrointestinal tract	312 (70.6%)
Appendicitis	133 (30.1)
Diverticulitis	75 (17)
Inflammatory bowel disease	10 (2.3)
Malignancy	18 (4.1)
Ischemic	39 (8.8)
Miscellaneous	37 (8.4)
Upper intestinal tract	130 (29.4)
Biliary tract	76 (17.2)
Ulcus disease	43 (9.7)
Ischemic	6 (1.4)
Miscellaneous	5 (1.0)

Whole cohort (n = 442)

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)

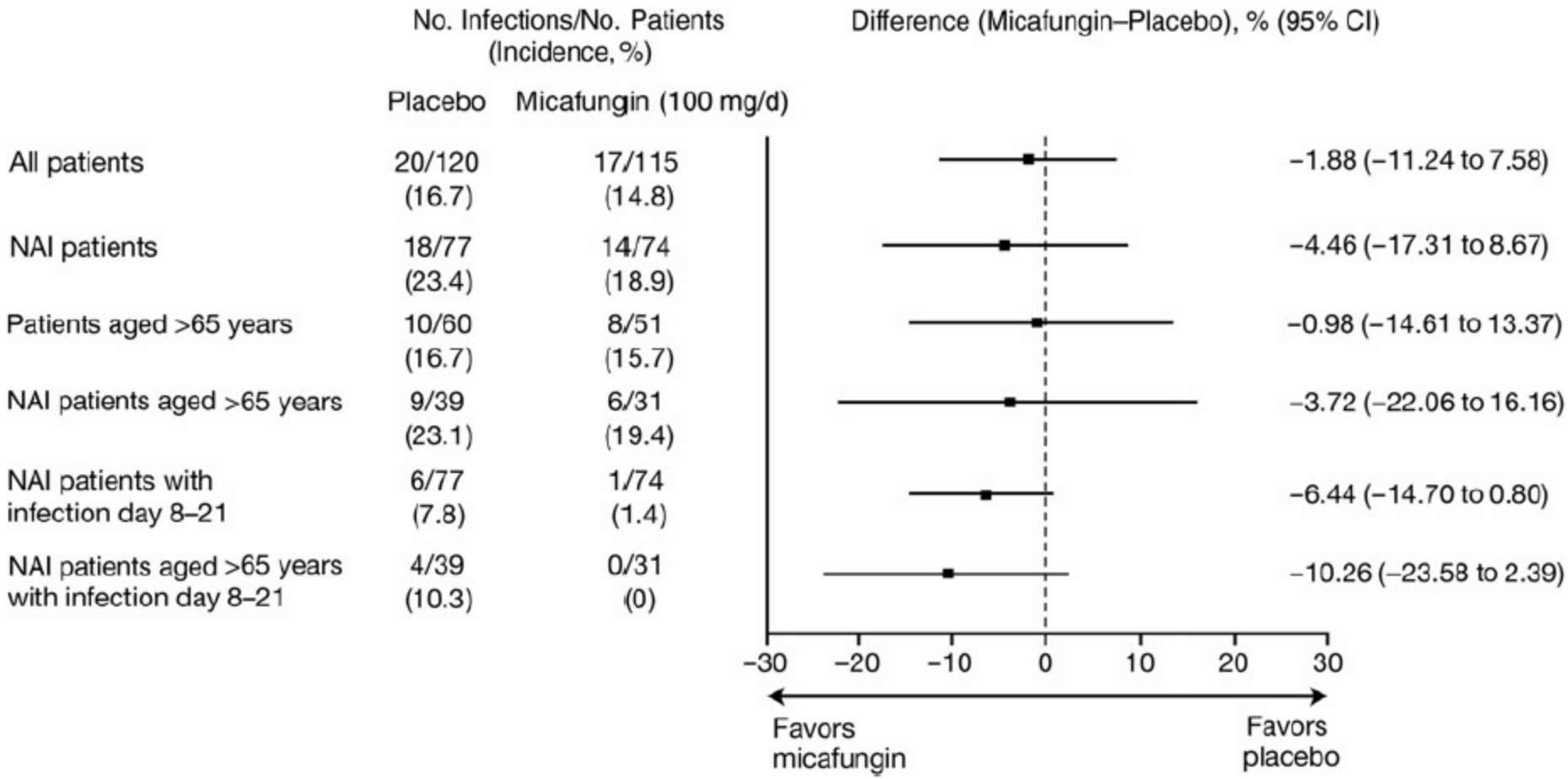
A Randomized, Placebo-controlled Trial of Preemptive Antifungal Therapy for the Prevention of Invasive Candidiasis Following Gastrointestinal Surgery for Intra-abdominal Infections. *Knitsch W et al, Clin Infect Dis 2015;61:1671-8*

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



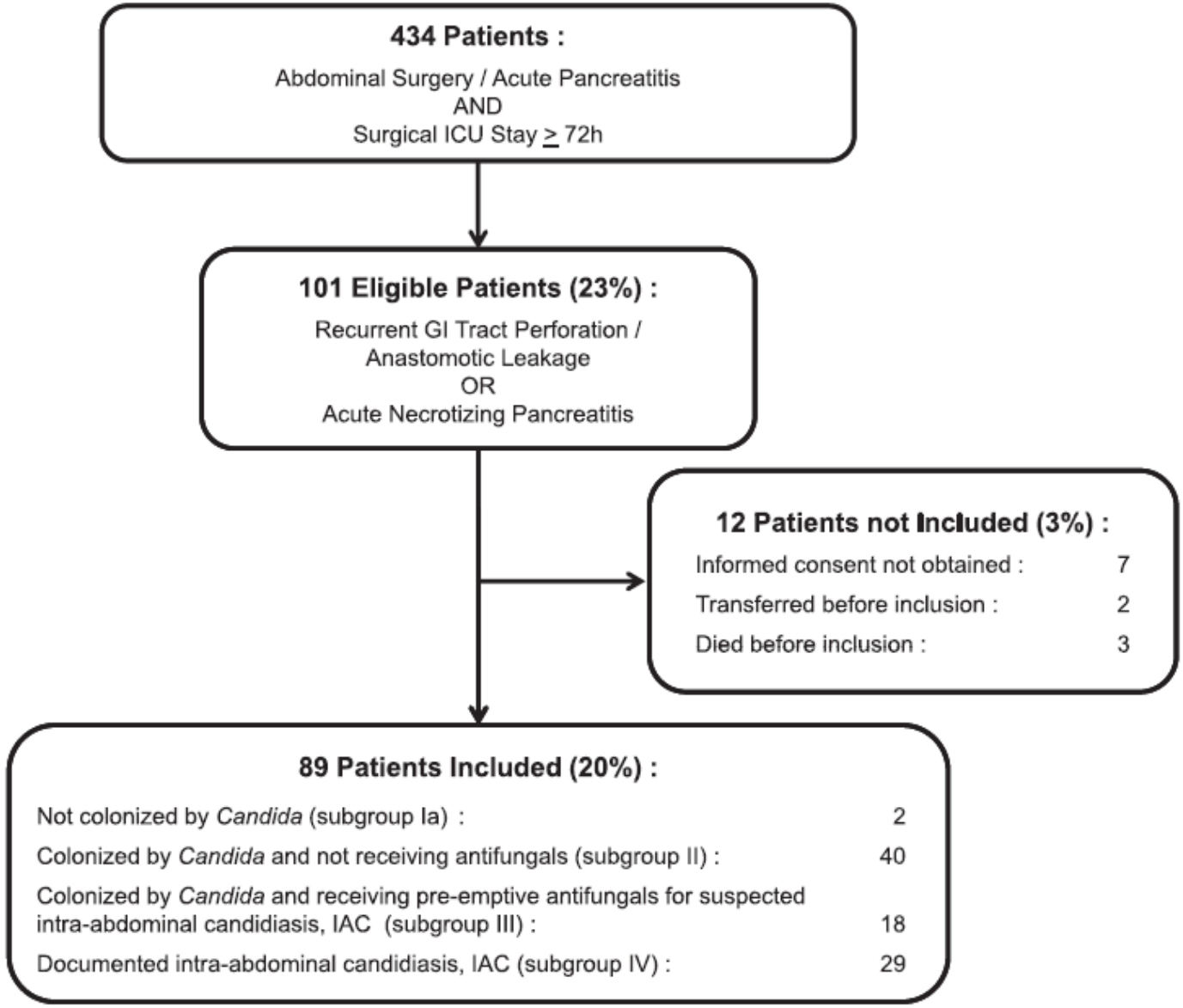
A Randomized, Placebo-controlled Trial of Preemptive Antifungal Therapy for the Prevention of Invasive Candidiasis Following Gastrointestinal Surgery for Intra-abdominal Infections. *Knitsch W et al, Clin Infect Dis 2015;61:1671-8*

This study was unable to provide evidence that preemptive administration of an echinocandin was effective in preventing IC in high-risk surgical intensive care unit patients with intra-abdominal infections.

The estimated odds ratio showed that patients with a positive (1,3)-β-D-glucan result were 3.66 (95% confidence interval, 1.01–13.29) times more likely to have confirmed IC than those with a negative result.

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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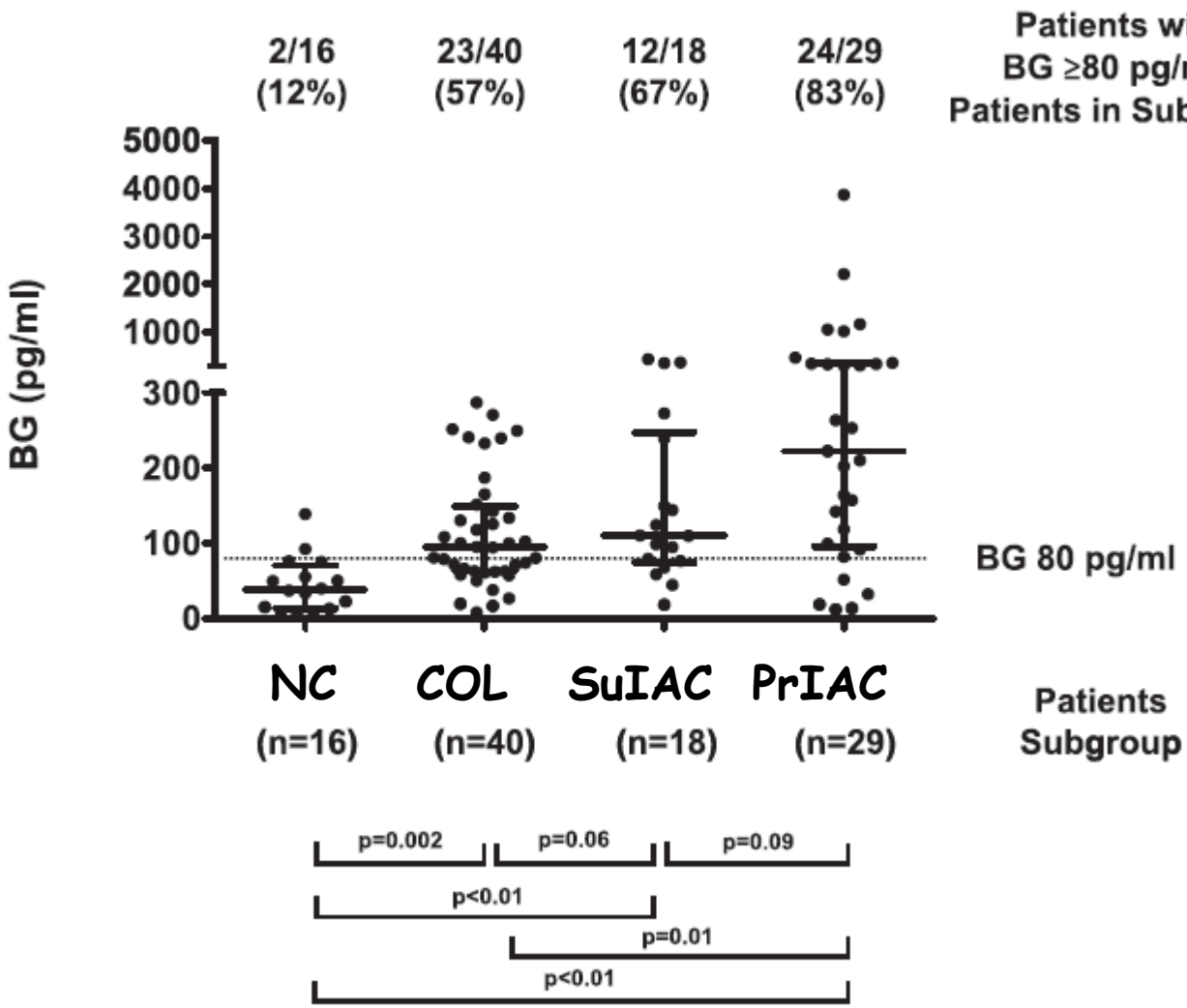


Median BDG

COLONIZED 99 pg/ml (8-440)

IAC 254 pg/ml (46-8557)

Can yeast isolation be predicted in complicated secondary non-postoperative intra-abdominal infections?

Dupont H et al. Critical Care 2015; 19:60

Gram-negative bacilli	426 (45.9%)
Gram-positive cocci	251 (27.1)
Anaerobes	178 (19.2)
Fungi	72 (7.7)
Candida albicans	47
Candida glabrata	8
Candida tropicalis	7
Candida krusei	3
Miscellaneous	7

Can yeast isolation be predicted in complicated secondary non-postoperative intra-abdominal infections?

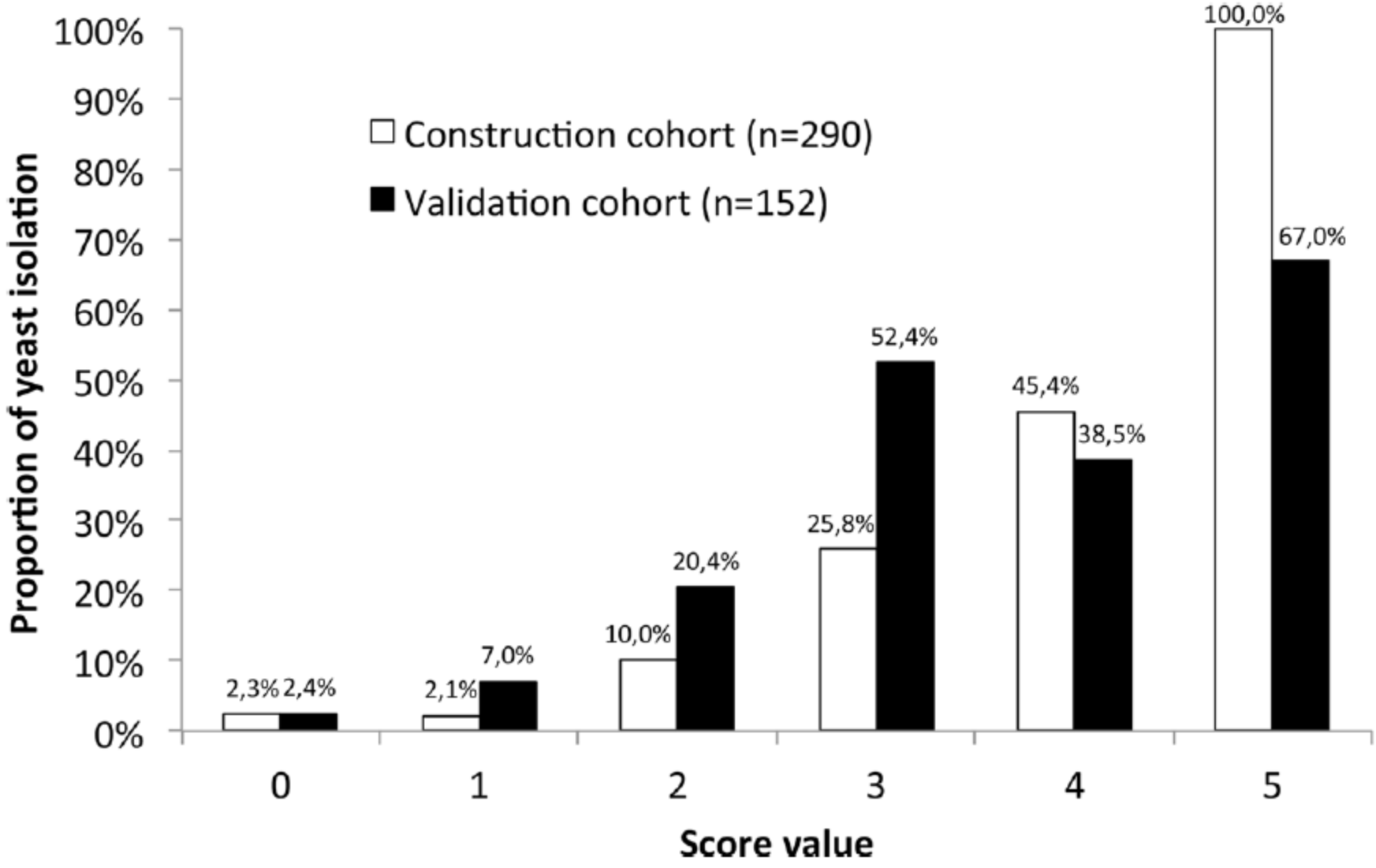
Dupont H et al. Critical Care 2015; 19:60

Multivariate analysis of factors independently associated with an intra-abdominal candidiasis in the retrospective cohort

Parameters	OR	95%CI	P	
Per-operative cardiovascular failure	2.43	1.01 - 5.81	0.04	1
Upper gastrointestinal tract perforation	2.53	1.15 - 5.55	0.02	1
LOS ≥48 h before surgery	3.15	1.45 - 6.89	0.004	1
Generalized peritonitis	6.78	2.75 - 16.68	<0.001	2

Can yeast isolation be predicted in complicated secondary non-postoperative intra-abdominal infections?

Dupont H et al. Critical Care 2015; 19:60



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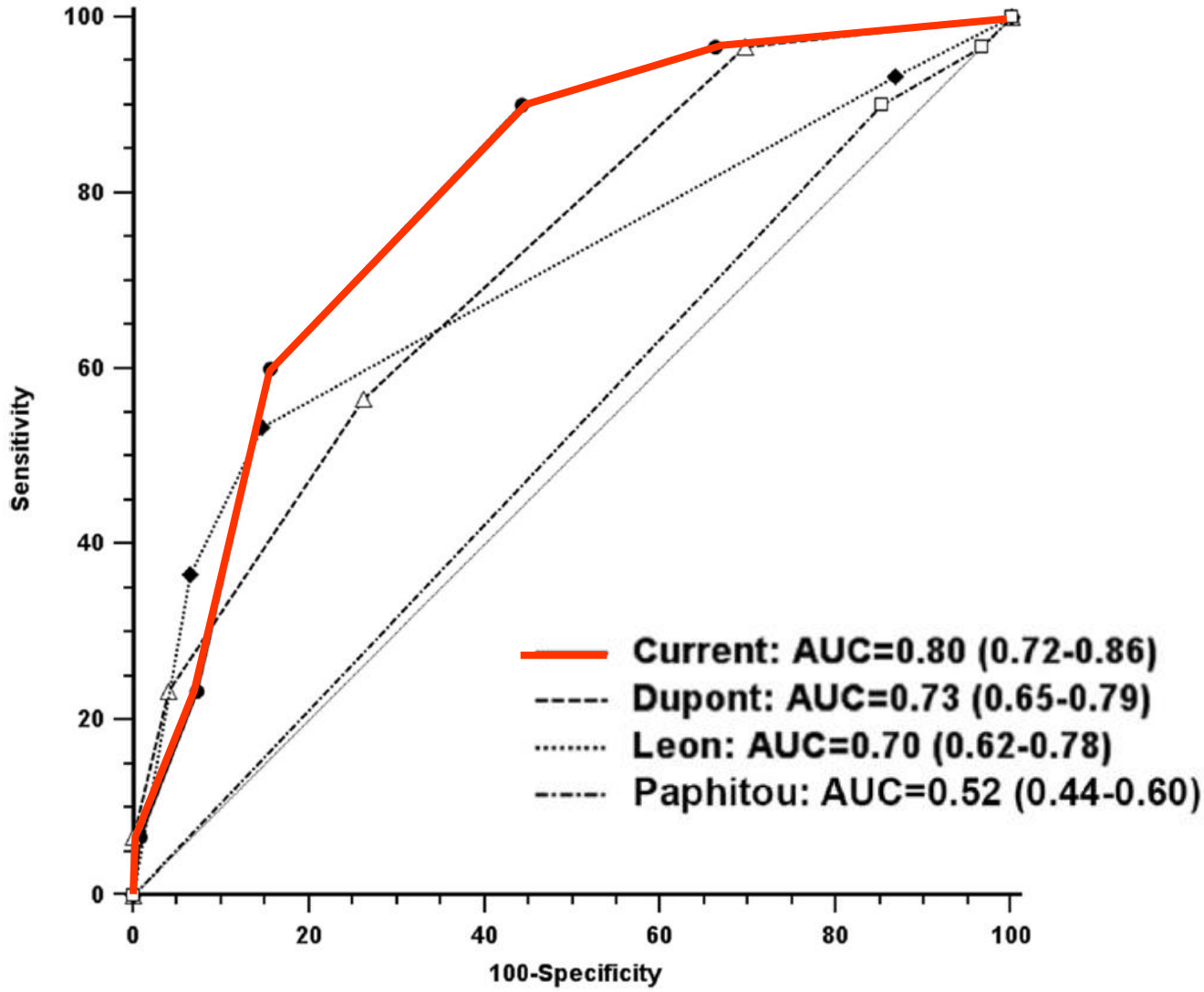


Can yeast isolation be predicted in complicated secondary non-postoperative intra-abdominal infections? *Dupont H et al. Critical Care 2015; 19:60*

Comparison of outcomes

	Yeast positive	Yeast negative	P value
ICU admission	39 (56.5)	111 (29.8)	<0.001
Duration of MV(d)	10.7 ± 14.9	9.5 ± 14.7	0.69
ICU LOS (d)	16.1 ± 16.	4 11.6 ± 13.9	0.11
Hospital LOS (d)	20.5 ± 22.	4 13.2 ± 16.0	0.001
Mortality	19 (27.5)	31 (8.3)	<0.001

WHICH DRUG FOR SUSPECTED/PROVEN IAC ?

The choice of the appropriate empirical antifungal agent for IAC is mainly supported by indirect evidence from studies on candidemia

ECHINOCANDINS

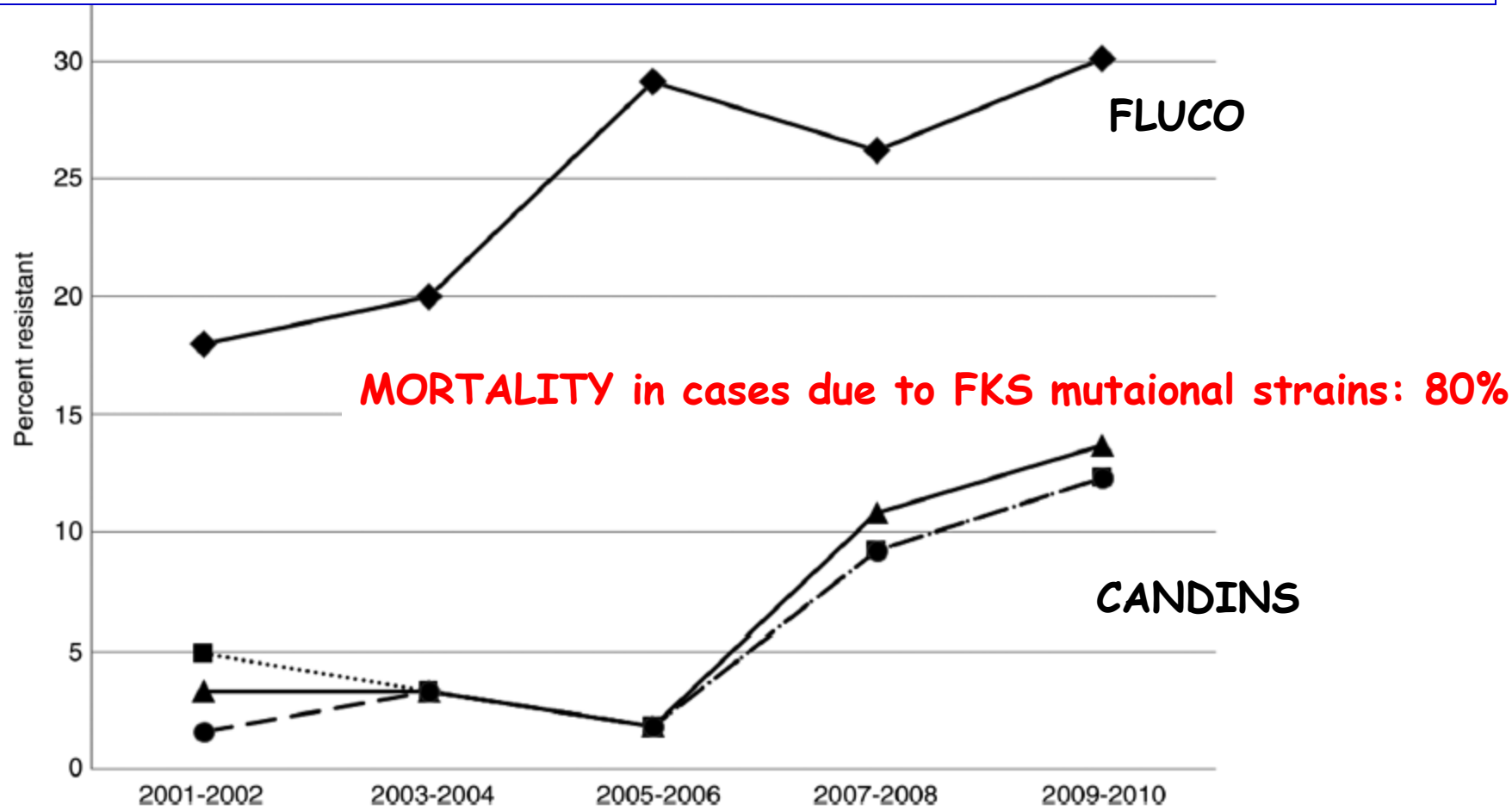
L-AMB

AZOLES

Increasing Echinocandin Resistance in Candida glabrata: Clinical Failure Correlates With Presence of FKS Mutations and Elevated Minimum Inhibitory Concentrations

Alexander BD et al, Clin Infect Dis 2013; 56:1724–32

Two hundred ninety-three episodes (313 isolates) of *C. glabrata* BSI from 2001 to 2010 – resistance trends



Abdominal candidiasis is a hidden reservoir of echinocandin resistance

Shields RK et al, Antimicrob. Agents Chemother, ahead of print on 6 October 2014

FKS mutant Candida were recovered from 24% (6/25) of echinocandin-exposed patients with abdominal candidiasis.

C. glabrata (29%) and _C. albicans_ (14%) mutants were identified.

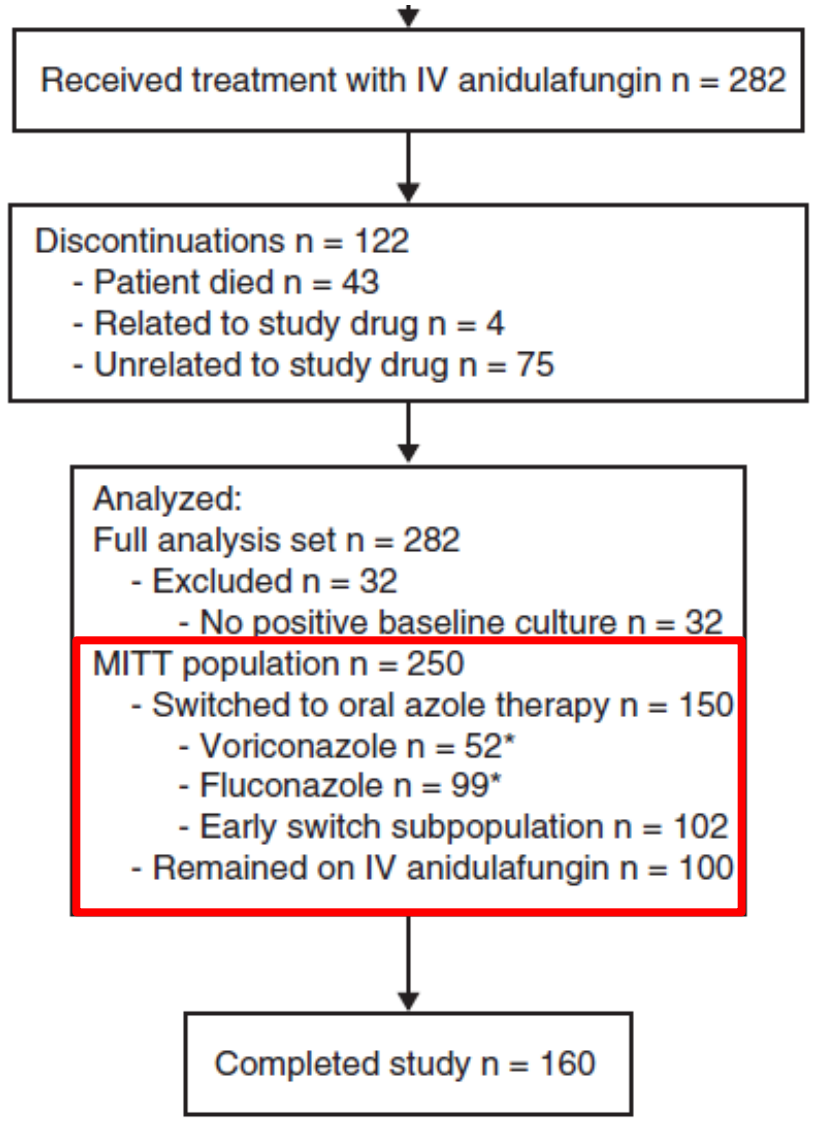
MDR resistant bacteria were recovered from 83% of _FKS_ mutant infections.

Mutations were associated with prolonged echinocandin exposure (p=0.01), breakthrough infections (p=0.03), and therapeutic failures despite source control interventions (100%).

Evaluation of an early step-down strategy from anidulafungin to oral azole therapy for the treatment of candidemia and other forms of invasive candidiasis: results from an open-label trial. *Vazquez J et al, BMC Infectious Diseases 2014, 14:97*

An open-label, non-comparative study evaluated an
strategy. Patients with C/IC were treated with IV
therapy had the option to step-down to oral azole
they met pre-specified criteria:

- ability to tolerate oral therapy;
- afebrile for > 24 hours;
- hemodynamically stable;
- not neutropenic;
- clearance of Candida from the bloodstream.



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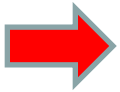
Response	MITT population (n = 250) n/N (%) [95% CI][a]	Early switch subpopulation (n = 102) n/N (%) [95% CI][a]
Global response at EOT	170/203 (83.7) [78.7–88.8]	81/ 90 (90.0) [83.8–96.2]
Success	170/250 (68.0) [62.2–73.8]	81/102 (79.4) [71.6–87.3]
Sensitivity analysis*		
Clinical response at EOT	174/187 (93.0) [89.4–96.7]	83/ 89 (93.3) [88.0–98.5]
Success	174/250 (69.6) [63.9–75.3]	83/102 (81.4) [73.8–88.9]
Sensitivity analysis*		
Microbiological response at EOT		
Success	183/192 (95.3) [92.3–98.3]	87/ 90 (96.7) [93.0–100.0]

INDICATION TO TREATMENT

DURATION OF TREATMENT

THE CONUNDRUM OF INTRA-ABDOMINAL CANDIDIASIS



THE ANTIBIOTIC CHOICE IN THE ERA OF ANTIBIOTIC CRISIS

PUTATIVE INDICATIONS OF NEW ANTIBIOTICS IN IAI

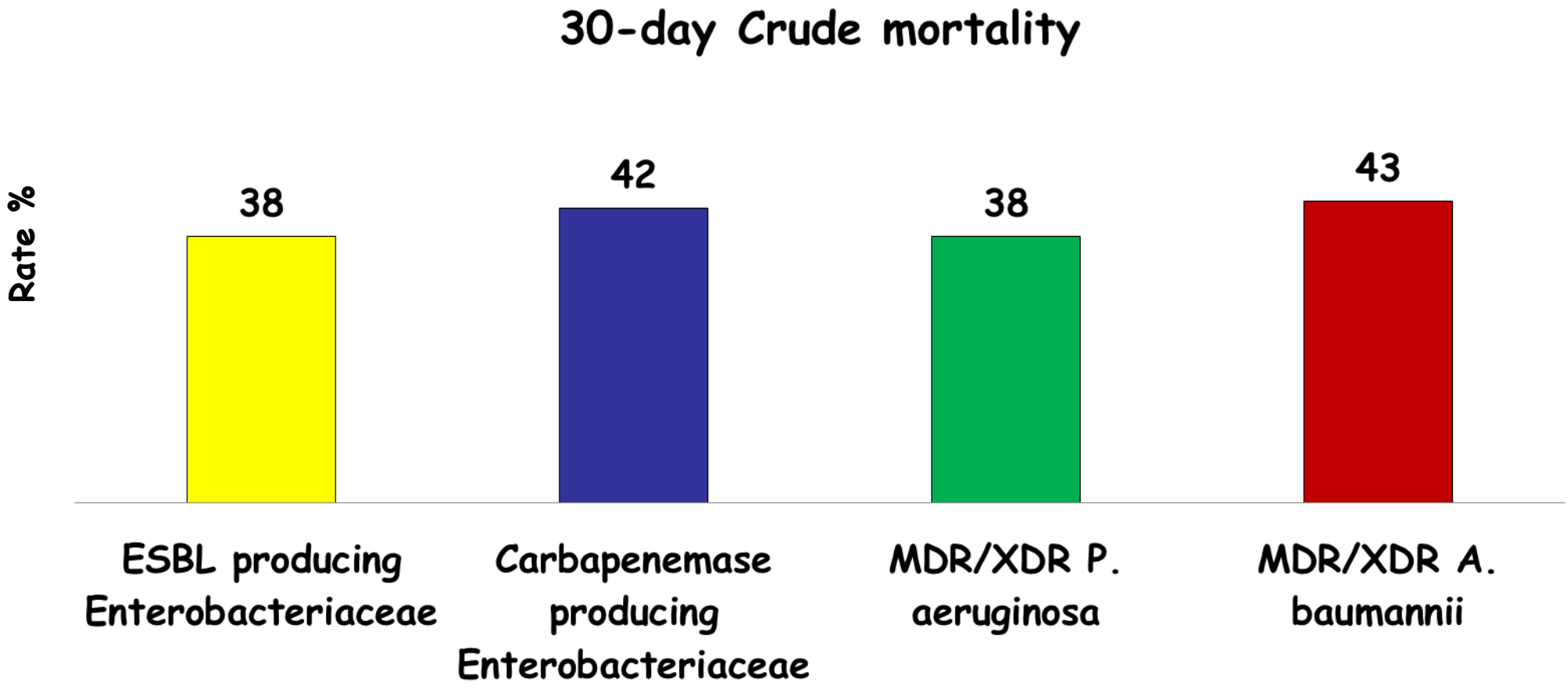
The ESKAPE gang

bacterial clones that:

- have acquired multiple resistance determinants (MDR/XDR phenotypes)
- retain a notable propensity for cross-transmission and spreading playing a relevant role in infections and in the dissemination of resistant determinants (low impact of resistance on epidemiological fitness → high epidemiological risk)
- are associated to significant morbidity and mortality (low impact of resistance on clinical fitness → high clinical risk)

Woodford et al - FEMS Microbiol Rev 2011

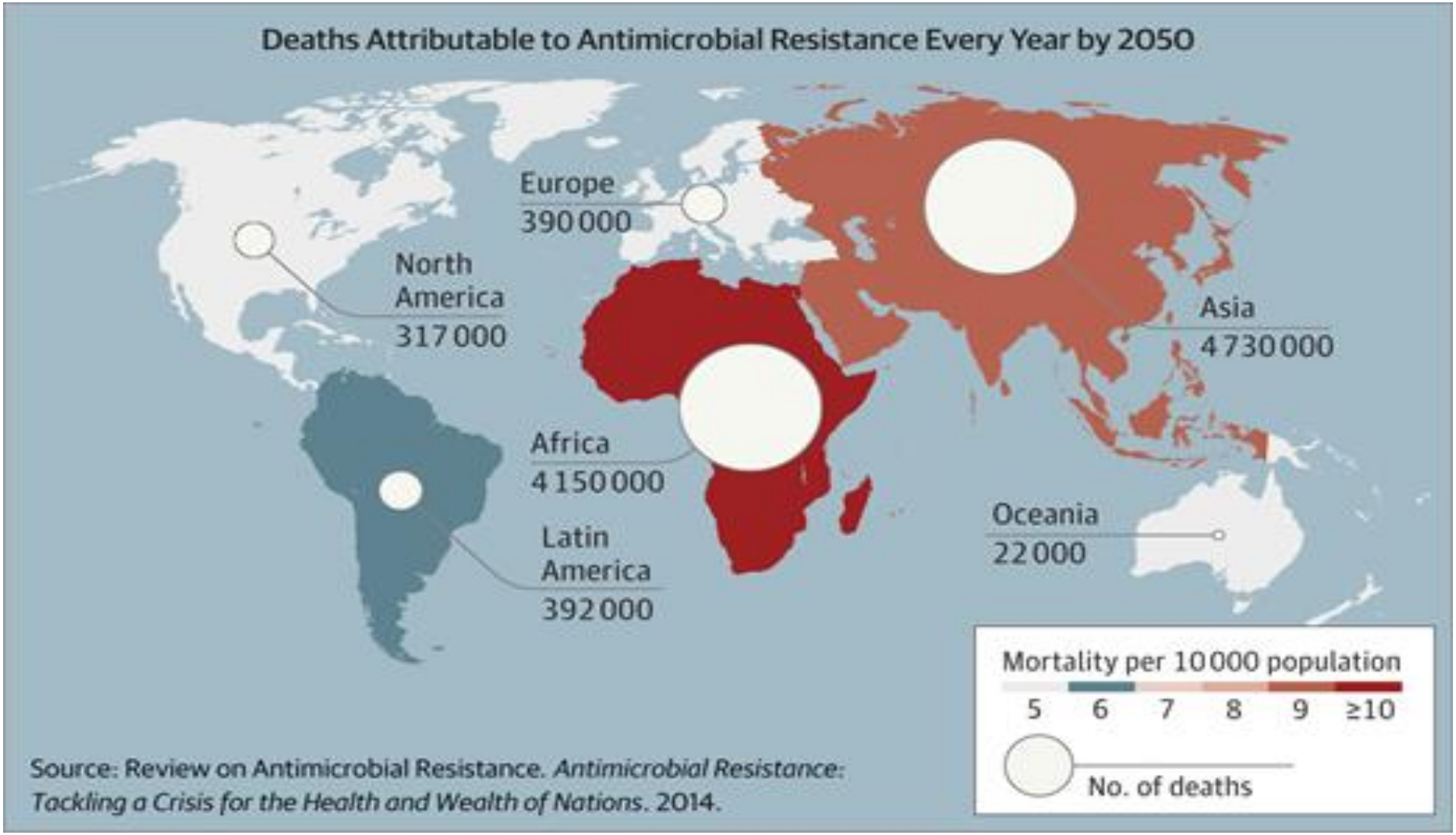
MDR GRAM NEG



Tumbarello M et al. Antimicrob Agents and Chemother 2007
Pena C et al.Clin Infect Dis 2013:57
De Rosa FG et al, Fut Microbiol 2015

Tumbarello M et al, Clin Infect Dis 2012
Durante Mangoni E et al. Clin Infect Dis 2013
Doy Y et al Semin Respir Crit Care Med 2015

Deaths attributable to antimicrobial resistance every year by 2050



JAMA. Published online June 03, 2015

MDR Enterobacteriaceae management – UNMET NEEDS

ESBL

Is there a residual role of BL-BLI or are we condemned to always use carbapenems?

KPC

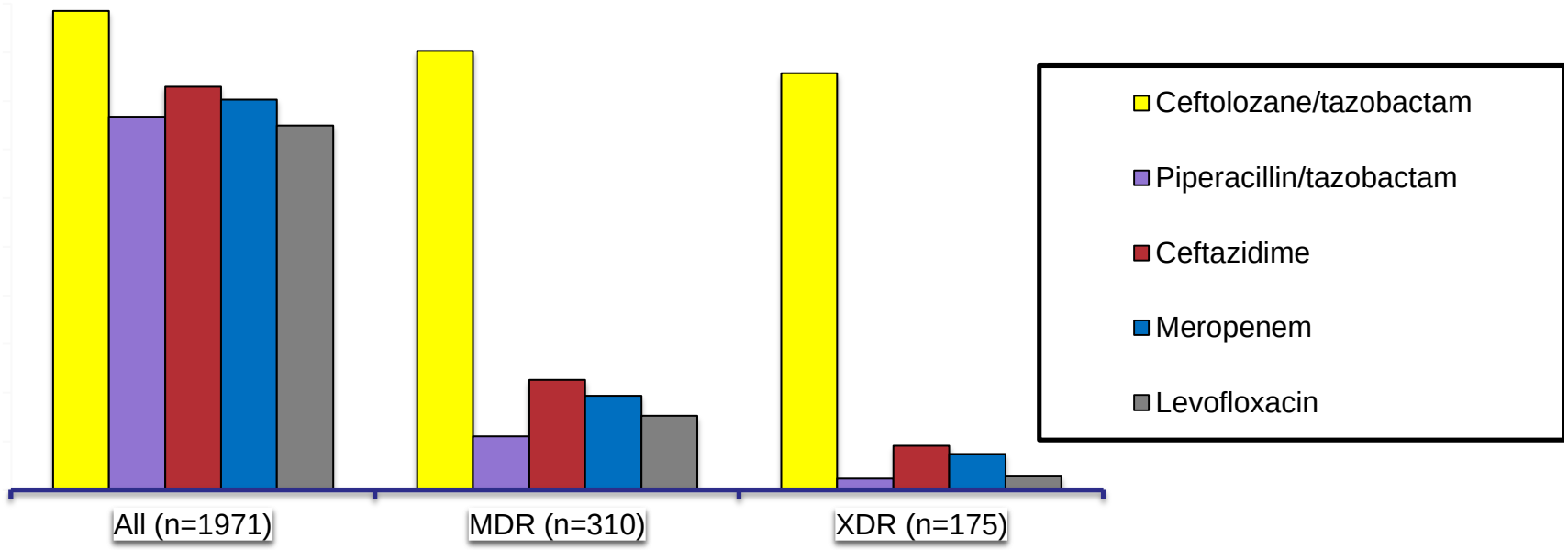
Data advocating the superiority of combo regimens are all derived from observational, uncontrolled studies. Therefore randomized clinical trials aimed at comparing Mono vs Combo and Different combo regimen could be strongly needed, if feasible.

Which is the best combo regimen and what is the role of carbapenems are two open questions

Of concern is the increasing number of reports documenting CPE resistance to colistin and tigecycline considered "salvage" agents for therapy. How these pandrug-resistant cases can be best managed remains an open question.

Are there settings or patients where an empirical anti CPE treatment should be prescribed?

In Vitro Activity of CEFTOLOZANE/TAZOBACTAM and Various Comparator Agents Against *P. aeruginosa* (US Hospitals 2011-2012)



	Ceftolozane/ tazobactam		Piperacillin/ tazobactam		Ceftazidime		Meropenem		Levofloxacin	
	MIC_{50}/MIC_{90}	%S*[a]	MIC_{50}/MIC_{90}	%S[b]	MIC_{50}/MIC_{90}	%S[b]	MIC_{50}/MIC_{90}	%S[b]	MIC_{50}/MIC_{90}	%S[b]
All (1971)	0.5/2	98.5	8/>64	76.8	2/32	82.9	0.5/8	80.3	0.5/>4	74.9
MDR (310)	2/8	90.3	>64/>64	11	32/>32	22.6	8/>8	19.4	>4/>4	15.2
XDR (175)	4/16	85.7	>64/>64	2.3	32/>32	9.1	8/>8	7.4	>4/>4	2.9

Farrell et al. Antimicrob Agents Chemother. 2013;57:6305-10.

CEFTAZIDIME-AVIBACTAM

Avibactam is a non–b-lactam b-lactamase inhibitor, acting against the activities of Ambler class A and C and some Ambler class D enzymes

- Through the addition of avibactam, ceftazidime's activity is expanded to many ceftazidime-resistant and carbapenem-resistant Enterobacteriaceae and P. aeruginosa. This includes isolates producing a variety of Ambler class A and C b-lactamases including AmpC, ESBLs, and KPC, as well as select class D OXA enzymes.

- In contrast, ceftazidime-avibactam does not possess any appreciable activity against the Ambler class B metallo–b-lactamases.

- FDA approved as rescue option for CIAI and cUTI

Successful Treatment of Carbapenemase-Producing Pandrug-Resistant *Klebsiella pneumoniae* Bacteremia

Camargo JF et al , Antimicrob Ag Chemother 2015; 59:5903–5908.

64-year-old female, intestinal transplanted

+12 pancreatitis with peri-pancreatic fluid collection → KPC-Kp isolated
The isolate was resistant to aminoglycosides but susceptible to tigecycline and colistin . The patient was started on a combination of tigecycline and colistin and completed a 14-day course

+ 36 HAP → KPC-Kp isolated from BAL
The isolate was now resistant to tigecycline but susceptible to colistin . The patient was started on a combination of colistin and extended-infusion

+ 65 which of the following therapeutic options could be more appropriate ?
A. Intravenous fosfomycin
B. Dual-carbapenem therapy
C. Ceftazidime-avibactam
D. Other (on fantasy)

+ 72 the patient was switched to a combination of colistin, meropenem , and ertapenem . She initially responded to this regimen but developed breakthrough bacteremia 12 days later. The isolate had now become resistant to colistin

Successful Treatment of Carbapenemase-Producing Pandrug-Resistant *Klebsiella pneumoniae* Bacteremia

Camargo JF et al , Antimicrob Ag Chemother 2015; 59:5903–5908.

Treatment with a combination of intravenous CAZ-AVI (1,000 mg/250 mg i.v. q8h based on the recommended dose determined by creatinine clearance and ertapenem (1 g i.v. q24h) was then started.

The patient responded well, with sterilization of her blood cultures within 24 h of this regimen.

She completed a course of 2 weeks and by the end of therapy, for the first time since her admission, was transferred out of the intensive care unit