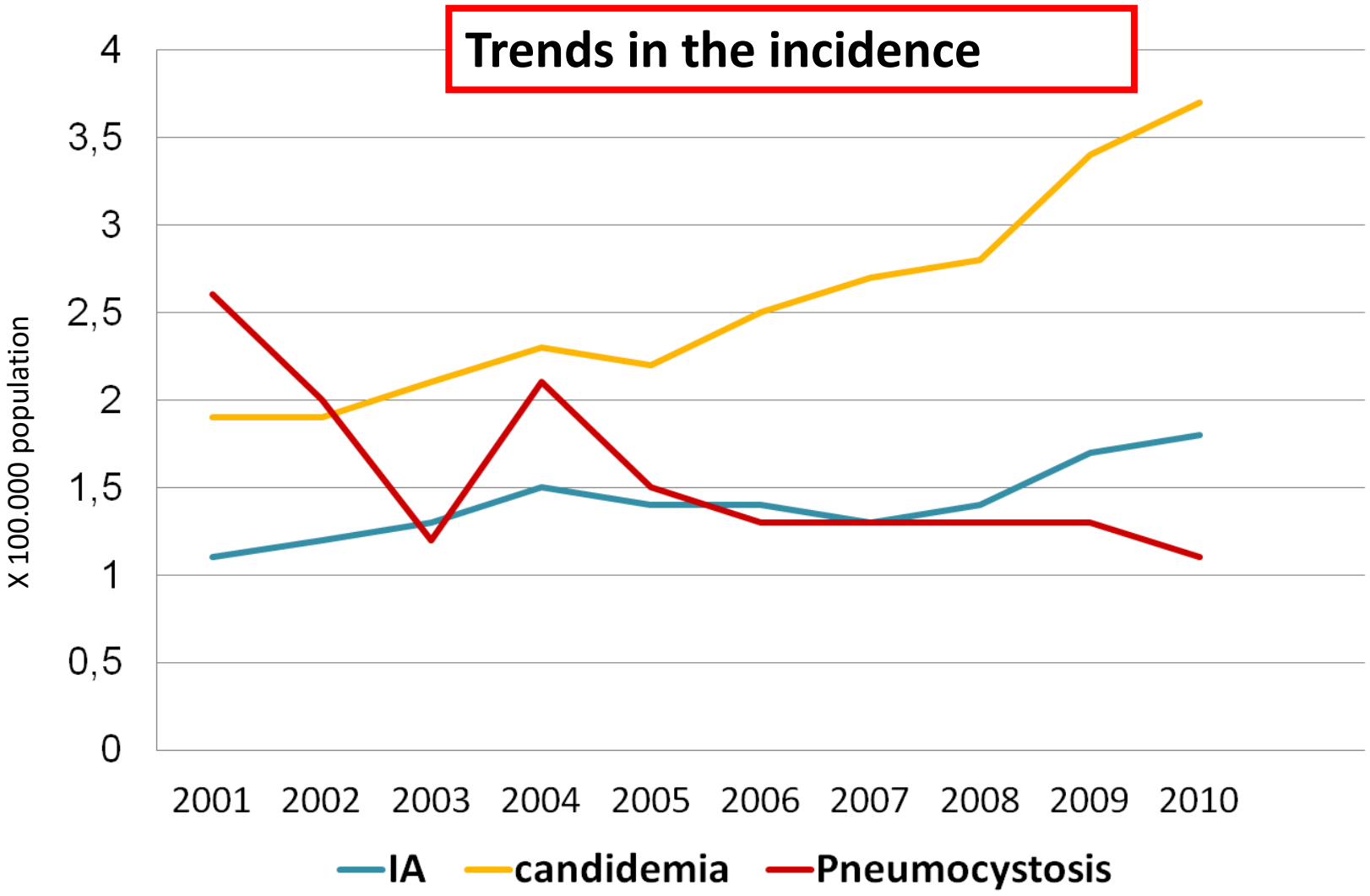
Le candidemie oggi: una gestione articolata

Michele Bartoletti Infectious Diseases Unit S. Orsola Teaching Hospital

Population-Based Analysis of Invasive Fungal Infections, France, 2001–2010

Bitar D et al. Emerg Infect Dis 2014;20:1149



Epidemiology and predictive factors for early and late mortality in Candida bloodstream infections: a population-based surveillance in Spain

Puig-Asensio et al.Clin Microbiol Infect 2014

Prospective, population-based study for *Candida* BSI in five metropolitan areas in Spain, between 2010-2011.

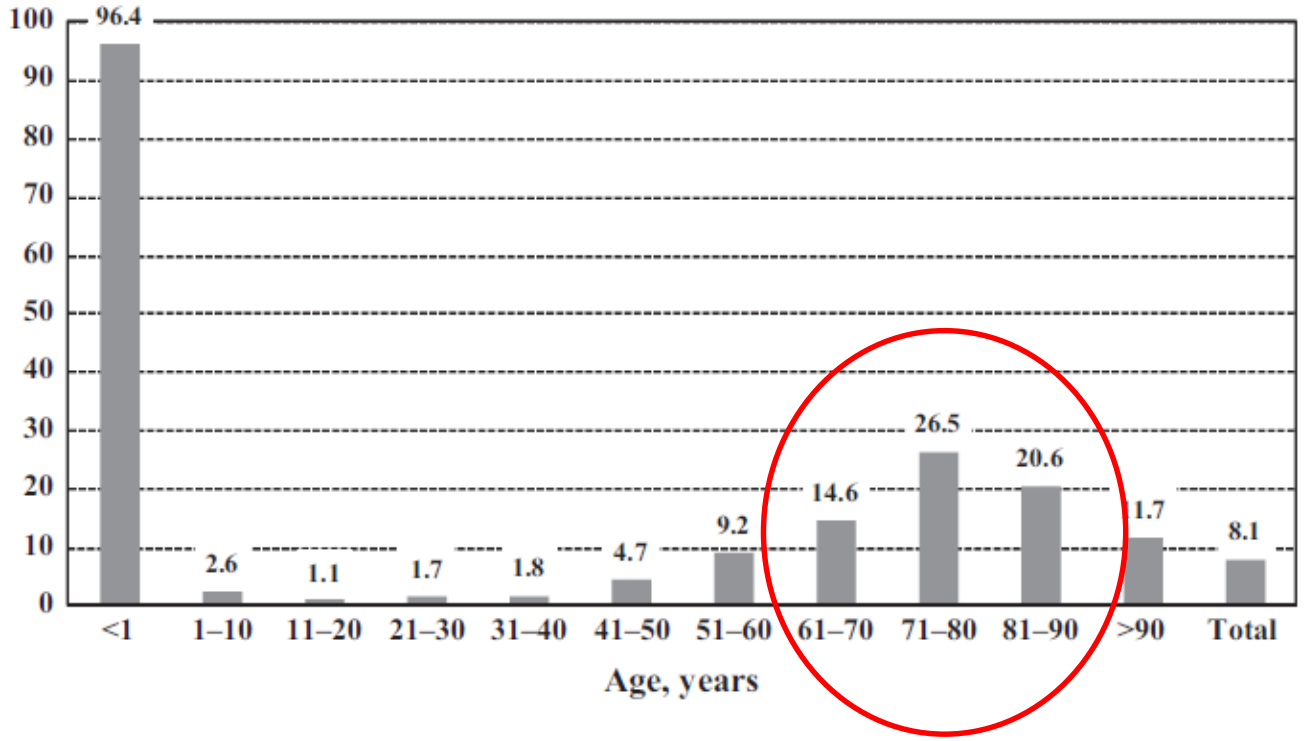
773 episodes, annual incidence

- **8.1 cases/100 000 inhabitants**
- **0.89/1000 admissions**
- **1.36/10 000 patient-days**

Epidemiology and predictive factors for early and late mortality in Candida bloodstream infections: a population-based surveillance in Spain

Puig-Asensio et al.Clin Microbiol Infect 2014

Candidemia incidence per 100 000 inhabitants



Epidemiology and predictive factors for early and late mortality in Candida bloodstream infections: a population-based surveillance in Spain

Puig-Asensio et al.Clin Microbiol Infect 2014

Overall 30-day mortality was 30.6%

Appropriate antifungal treatment within the first 48 h was the only factor independently associated with lower early (0-7 days) mortality (OR 0.35, 95% CI 0.20–0.61).

In patients with CVC adequate antifungal treatment (OR 0.51, 95% CI 0.27–0.95) and having the CVC removed (OR 0.43, 95% CI 0.21–0.87) within the first 48 h remained associated with decreased early mortality.

Independent risk factors for late mortality were related to host characteristics (age, immunosuppression), clinical presentation of candidaemia with septic shock or severe sepsis (OR 1.77, 95% CI 1.05–3.00) and primary infection (OR 1.63, 95% CI 1.03–2.61).

Epidemiology, Species Distribution, Antifungal Susceptibility and Outcome of Candidemia across five sites in Italy and Spain

M . Bassetti et al, J Clin Microbiol 2013

995 candidemia episodes in five hospitals in Italy and Spain from 2008 to 2010

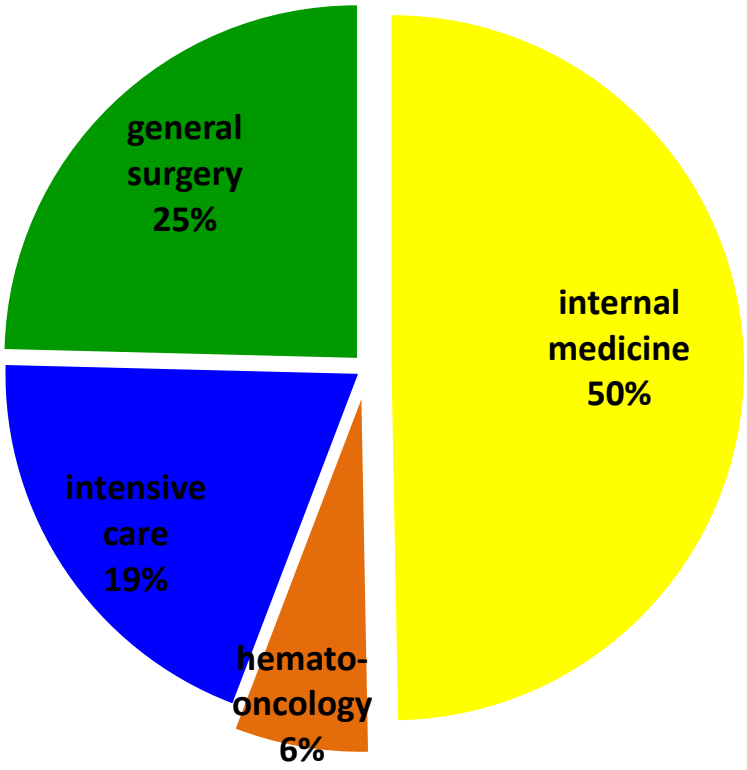
Incidence was 1.55 cases per 1000 admissions and remained stable

	Mean incidence (no. of episodes/1,000 admissions) by period:			
	2008	**2009**	**2010**	**2008-2010**
Udine	0.73	0.79	0.84	0.8
Trieste	2.11	1.73	1.4	1.74
Rome	2.35	2.53	2.71	2.53
Barcelona	1.6	1.57	1.54	1.55
Seville	0.98	1.08	1.25	1.12
Overall	1.55	1.54	1.71	1.55

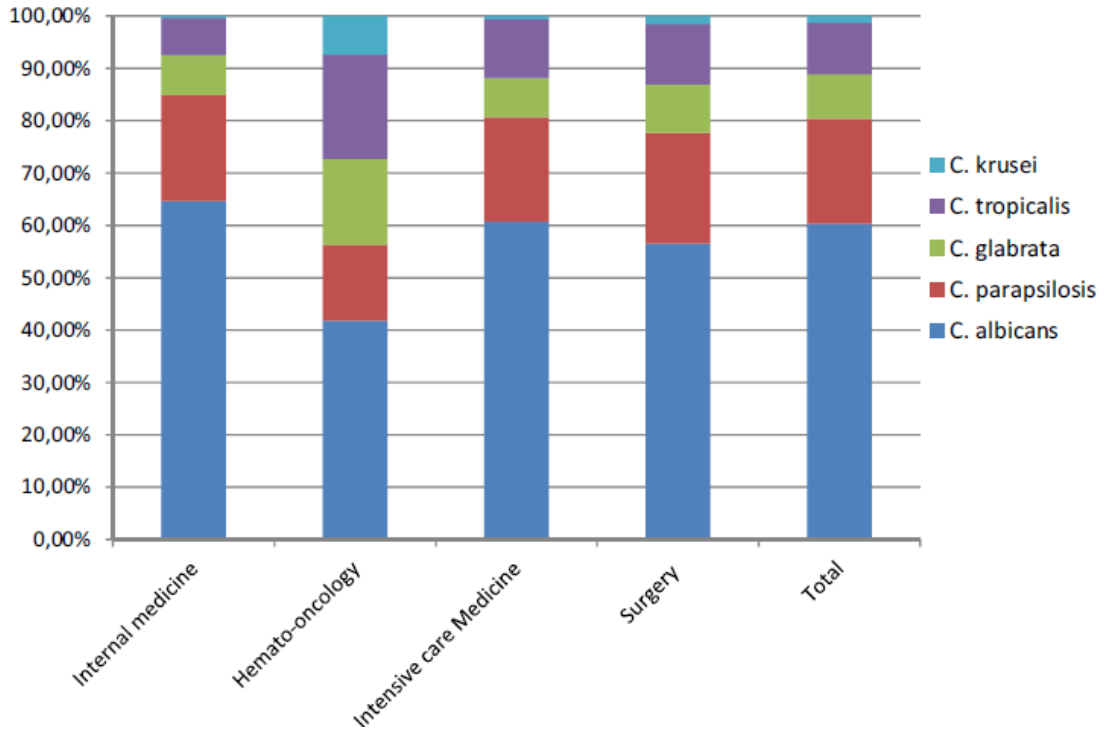
Epidemiology, Species Distribution, Antifungal Susceptibility and Outcome of Candidemia across five sites in Italy and Spain

M . Bassetti et al, J Clin Microbiol 2013

Candidemia distribution in hospital wards



Species distribution

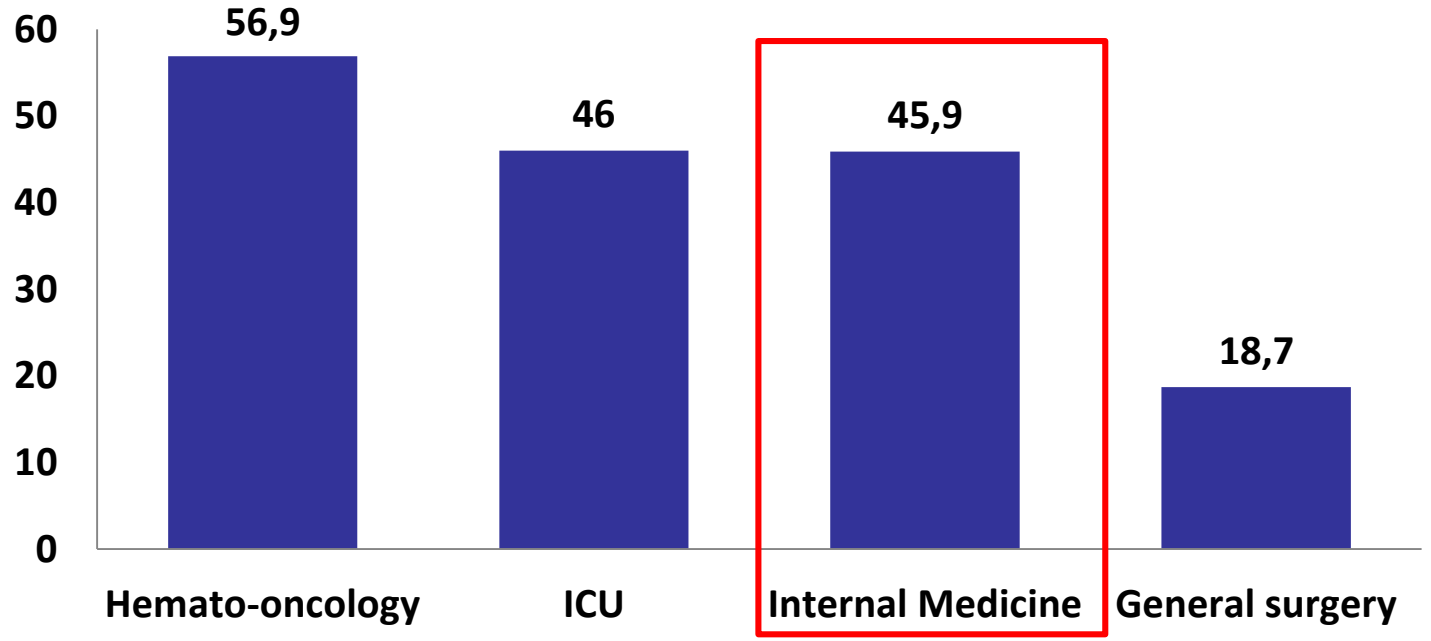


Epidemiology, Species Distribution, Antifungal Susceptibility and Outcome of Candidemia across five sites in Italy and Spain

M . Bassetti et al, J Clin Microbiol 2013

Overall 30-days mortality 39.9%

Important differences were noted between institutions: (33.6% and 51%; p=0.0005).



Candidaemia in internal medicine departments: the burden of a rising problem

M.Bassetti at al, CMI 2013

137 candidemia episodes observed in Internal Medicine Wards from 2008 to 2010 at S.Martino teaching hospital, Genova.

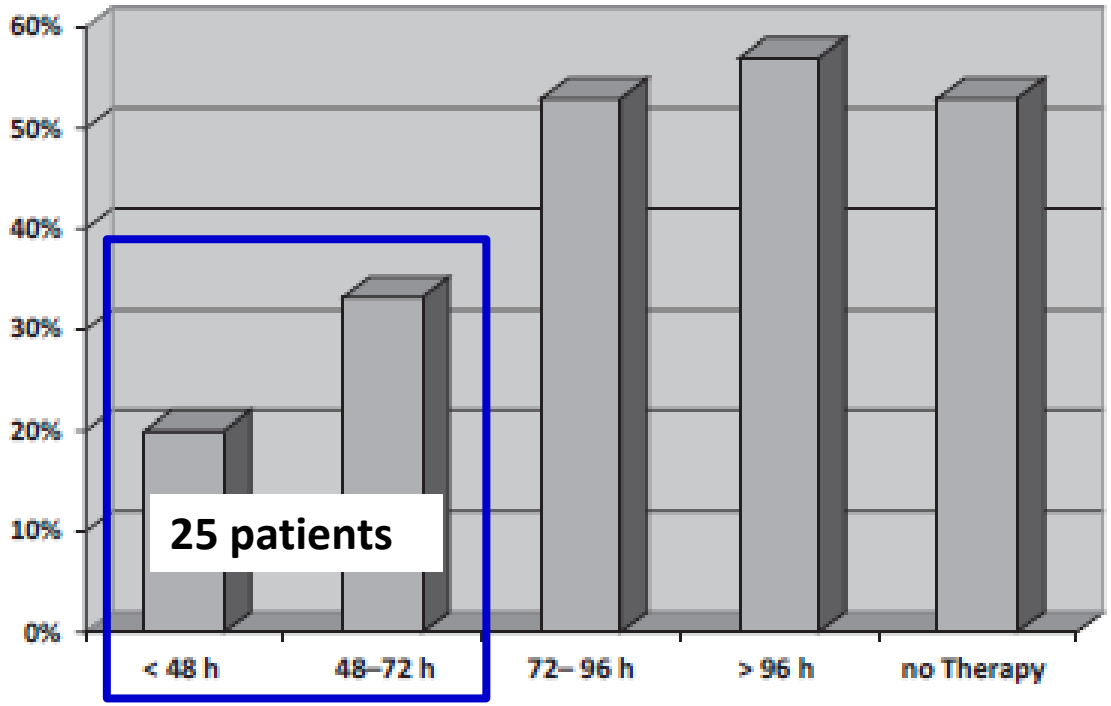
Variable	IMD (n = 137)	Others (n = 208)	p value
C. albicans (%)	65 (47.4)	105 (50.5)	0.581
C. parapsilosis	40 (29.2)	58 (27.9)	0.791
C. tropicalis	**16 (11.7)**	**7 (3.4)**	**0.002**
Age > 75 years (%)	**71 (51.8)**	**59 (28.4)**	**<0.001**
Urinary catheter (%)	**97 (70.8)**	**82 (39.4)**	**<0.001**
Renal failure (%)	45 (32.8)	57 (27.4)	0.281
Antibiotics prior month (%)	**100 (73)**	**107 (51.4)**	**<0.01**
Solid tumour (%)	**71 (51.8)**	**42 (20.2)**	**<0.001**
Days of hospital stay (range)	28.4 (13–96)	19.2 (12–115)	0.113
Parenteral nutrition (%)	**108 (78.8)**	**93 (44.7)**	**<0.005**
Central venous catheter (%)	**111 (81)**	**117 (56.3)**	**<0.01**
Diabetes (%)	39 (28.5)	52 (25)	0.475

Candidaemia in internal medicine departments: the burden of a rising problem

M.Bassetti at al, CMI 2013

30-days crude mortality 50.4%

Hospital mortality and timing of antifungal treatment.

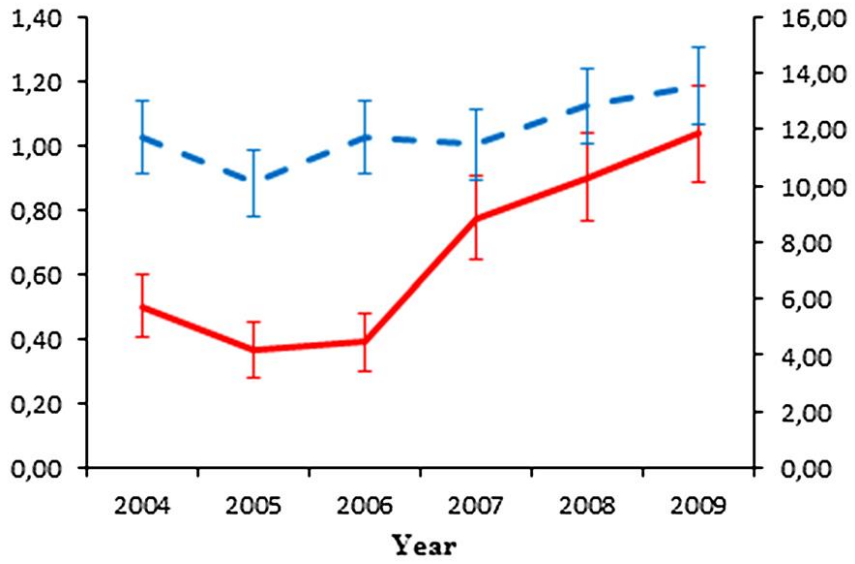


Worrisome trends in incidence and mortality of candidemia in intensive care units (Paris area, 2002–2010)

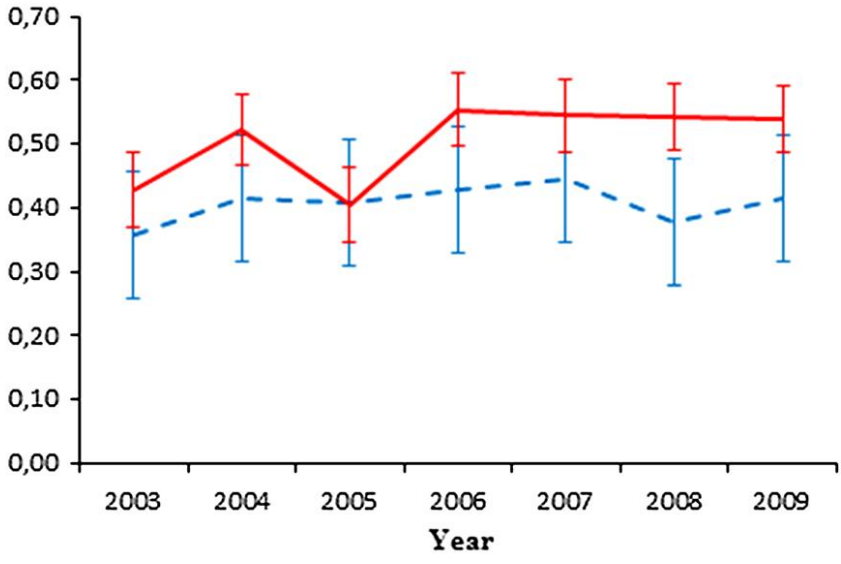
O . Lortholary et al, Intensive Care Med 2014

Active hospital-based surveillance program of incident episodes of candidemia in 24 tertiary care hospitals in the Paris area (Oct 2002-Sep 2010). 2507 adult patients included, 1206 (48%) in the ICU

Incidence by 10000 hospitalization days



Death rate at day 30 (%)



Patients hospitalized in ICU — All patients

Worrisome trends in incidence and mortality of candidemia in intensive care units (Paris area, 2002–2010)

O . Lortholary et al, Intensive Care Med 2014

Table 2 Risk factors for death in adult patients hospitalized in intensive care unit (ICU) with incident candidemia due to a single isolate (logistic regression), YEASTS program, Paris area, October 2002 to September 2010

	Death before day 30			Death before day 8			Death between day 8 and day 30		
	Adj. OR	95 % CI	*p*	Adj. OR	95 % CI	*p*	Adj. OR	95 % CI	*p*
Male gender							0.71	0.51–0.99	0.043
Age categories									
<45 years	1		0.0001				1		0.0003
45–64 years	1.66	1.09–2.53					2.32	1.38–3.89	
65–79 years	2.49	1.60–3.56					3.19	1.88–5.43	
≥80 years	3.09	1.73–5.49					2.91	1.45–5.83	
Arterial catheter	1.39	1.01–1.92	0.0430				1.47	1.02–2.11	0.0371
Sur									4
Spe									
C.									
C.									
C. parapsilosis									
C. tropicalis	0.99	0.61–1.63		1.00	0.53–1.86				
C. krusei	1.78	0.71–4.47		1.55	0.57–4.23				
C. kefyr	3.88	1.14–13.26		2.79	0.84–9.21				
Preexposure to caspofungin	3.83	1.29–11.35	0.0153	3.54	1.09–11.53	0.0357			
First-line treatment									
Fluconazole	1		0.0003	1		<0.0001			
Echinocandin	1.23	0.85–1.80		0.98	0.59–1.61				
Other treatment	1.11	0.69–1.79		0.81	0.42–1.56				
No treatment	4.34	2.23–8.45		11.04	5.72–21.30				

The factor associated with the highest odds of death (11.04) was lack of initial antifungal treatment when considering early death before day 8

IL PROBLEMA CANDIDEMIA: TERAPIA

EMPIRICA

NON NEUTROPENIC PATIENTS

	ESCMID 2012	ITALIC 2013	IDSA 2016
Prophylaxis	Question not been sufficiently addressed in clinical trials. Fluconazole prophylaxis is recommended in patients who recently underwent abdominal surgery and had recurrent gastrointestinal perforations or anastomotic leakages	Antifungal prophylaxis should not be administered in non-immunocompromised patients. The administration of an antifungal in complicated surgical patients, should not be defined as prophylaxis but rather as an empirical, presumptive or pre-emptive therapy.	Fluconazole could be used in high-risk patients in adult ICUs with a high rate (>5%) of invasive candidiasis (*weak recommendation; moderate-quality evidence*). An alternative is to give an echinocandin (*weak recommendation; low-quality evidence*).
Empiric treatment	Early treatment of presumed fungaemia is presumably associated with higher survival rates, but the optimal time point for initiating empiric antifungal treatment remains undetermined.	The decision of starting an antifungal therapy in the absence of a positive culture should be based on estimation of the individual risk based on criteria or scores stemming from multi-variable analyses and validated prospectively	Empiric antifungal therapy should be considered in critically ill patients with risk factors for invasive candidiasis and no other known cause of fever and should be based on clinical assessment of risk factors, surrogate markers for invasive candidiasis, and/or culture data from non sterile sites.

RISK FACTORS FOR INVASIVE CANDIDIASIS

Hospitalization in ICU
Acute/chronic organ dysfunction requiring intensive care/invasive procedures
Solid organ transaplantation
Onco-hematological diseases (and type) and HSCT, especially with GVHD
Surgery (especially abdominal and revision), trauma and burn patients
Pediatric and neonatal ICU
Multiple underlying medical conditions
Immunosuppressive therapy
Renal failure requiring hemodialysis and hemofiltration
Neutropenia
APACHE score
Multiple site colonisation
Duration of hospital stay
Previous history of candida infection
Parenteral nutrition and use of indwelling catheters
Diabetes mellitus
Previous prolonged antibiotic therapy

An Italian consensus for invasive candidiasis management.

L. Scudeller et al. Infection 2013

Candida Colonization and Subsequent Infections in Critically Ill Surgical Patients

D. Pittet et al, Ann Sur 1994

A 6-month prospective cohort study on patients admitted to the surgical and neonatal intensive care units in a 1600-bed university medical center (Geneva, Switzerland).

29/650 patients had Candida spp isolated in three or more samples taken from the same or different body sites on at least 2 consecutive screening days.

COLONIZATION INDEX indicates the number of positive sites colonized with Candida divided by the number of sites sampled. A threshold of ≥0.5 properly identified the infected patients.

CORRECTED COLONIZATION INDEX indicates the number of heavily colonized sites (use of semiquantitative culture) divided by the number of sites sampled. A threshold of ≥ 0.4 properly identified the infected patients.

A bedside scoring system ("Candida score") for early antifungal treatment in nonneutropenic critically ill patients with Candida colonization

C.Leon et al, Crit Care Med 2006

Objective: To obtain a score for deciding early antifungal treatment when candidal infection is suspected in nonneutropenic critically ill patients.

Design: Analysis of data collected from the database of the EPCAN project, a prospective, cohort, observational, multicenter surveillance study of fungal infection and colonization in ICU.

Setting: 73 medical-surgical ICUs of 70 teaching hospitals in Spain.

Patients: 1,699 ICU adult patients admitted from May 1998 to January 1999

Table 4. Calculation of the Candida score: Variables selected in the logistic regression model

Variable	Coefficient (β)	Standard Error	Wald χ^2	*p* Value
Multifocal *Candida* species colonization	1.112	.379	8.625	.003
Surgery on ICU admission	.997	.319	9.761	.002
Severe sepsis	2.038	.314	42.014	.000
Total parenteral nutrition	.908	.389	5.451	.020
Constant	−4.916	.485	102.732	.000

Multicenter retrospective development and validation of a clinical prediction rule for nosocomial invasive candidiasis in the intensive care setting

L. Ostrosky-Zeichner et al, Eur J Clin Microbiol Infect Dis 2007

Objective: To create a rule that identifies subjects at high risk for invasive candidiasis in the intensive care setting.

Design: Retrospective review and statistical modelling were carried out on 2,890 patients who stayed at least 4 days in 9 hospitals in the USA and Brazil

THE BEST PERFORMING RULE WAS AS FOLLOWS:

Any systemic antibiotic OR presence of CVC
AND
at least TWO of the following:
total parenteral nutrition
any dialysis
any major surgery
pancreatitis
any use of steroids
use of other immunosuppressive agents

Empirical Micafungin Treatment and Survival Without Invasive Fungal Infection in Adults With ICU-Acquired Sepsis, Candida Colonization, and Multiple Organ Failure. The EMPIRICUS Randomized Clinical Trial

FJ Timsit et al, JAMA 2016

Objective: To determine whether empirical micafungin reduces invasive fungal infection (IFI)–free survival at day 28.

Design, setting, and participants: Multicenter double-blind placebo-controlled study of 260 non-neutropenic, non-transplanted, critically ill patients with ICU-acquired sepsis, multiple Candida colonization, multiple organ failure, exposed to broad-spectrum antibacterial agents, and enrolled between July 2012 and February 2015 in 19 French ICUs.

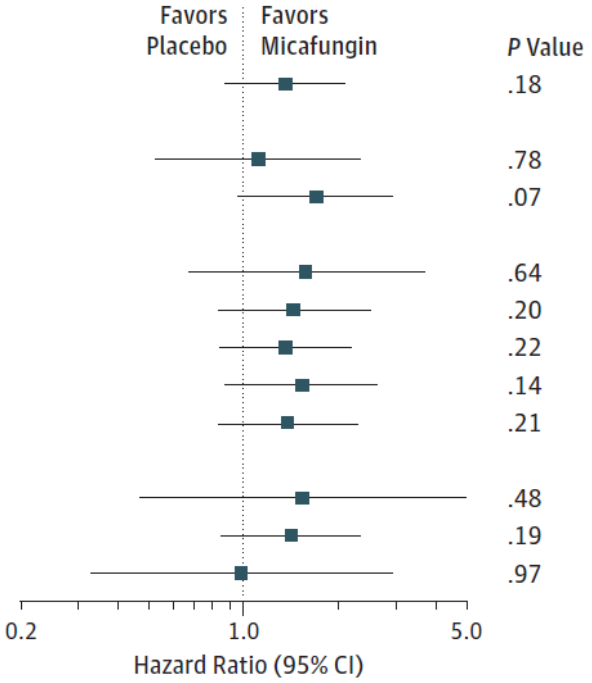
Interventions: **Empirical treatment with micafungin (100mg, once daily, for 14 days) (n=131) vs placebo (n=129).**

Empirical Micafungin Treatment and Survival Without Invasive Fungal Infection in Adults With ICU-Acquired Sepsis, Candida Colonization, and Multiple Organ Failure. The EMPIRICUS Randomized Clinical Trial

FJ Timsit et al, JAMA 2016

Figure 2. Comparison of Fungal Infection–Free Survival at Day 28 in the Modified Intent-to-Treat Population and in Predefined Subgroups

	Micafungin		Placebo			
	Survived at Day 28, No.	Total No.	Survived at Day 28, No.	Total No.	Hazard Ratio (95% CI)	*P* Value
All patients	87	128	74	123	1.35 (0.87-2.08)	.18
SOFA score						
≤8	51	66	52	68	1.11 (0.53-2.33)	.78
>8	36	62	22	55	1.69 (0.96-2.94)	.07
Admission category						
Surgical	22	34	16	31	1.56 (0.67-3.70)	.64
Medical	65	94	58	92	1.43 (0.83-2.50)	.20
Colonization index ≥0.5[a]	68	101	58	99	1.35 (0.84-2.17)	.22
Corrected colonization index ≥0.4[b]	52	76	45	80	1.52 (0.87-2.63)	.14
Candida score ≥3	64	96	47	85	1.37 (0.83-2.27)	.21
(1-3)-ß-D-glucan, pg/mL[c]						
>250	14	21	14	25	1.52 (0.47-5.00)	.48
>80	58	91	47	84	1.41 (0.85-2.33)	.19
≤80	29	37	27	39	0.98 (0.30-2.94)	.97

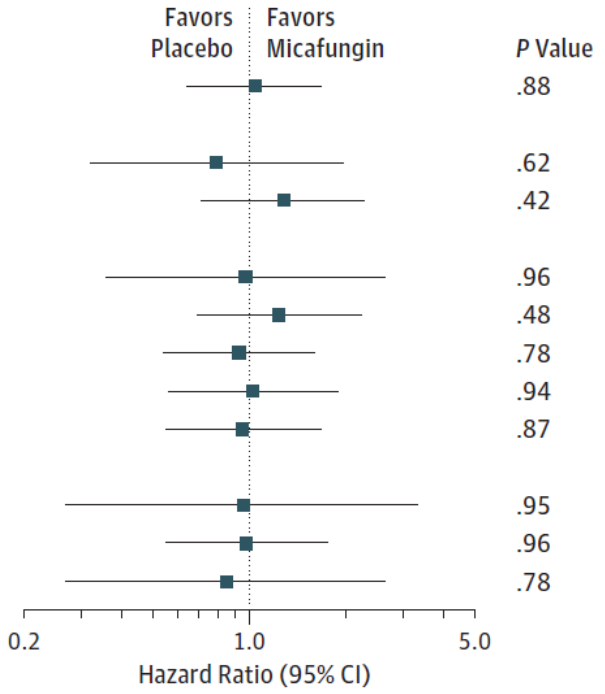


Empirical Micafungin Treatment and Survival Without Invasive Fungal Infection in Adults With ICU-Acquired Sepsis, Candida Colonization, and Multiple Organ Failure. The EMPIRICUS Randomized Clinical Trial

FJ Timsit et al, JAMA 2016

Figure 3. Comparison of Survival at Day 28 in the Modified Intent-to-Treat Population and in Predefined Subgroups

	Micafungin		Placebo			
	Survived at Day 28, No.	Total No.	Survived at Day 28, No.	Total No.	Hazard Ratio (95% CI)	*P* Value
All patients	90	128	86	123	1.04 (0.64-1.67)	.88
SOFA score						
≤8	53	66	58	68	0.79 (0.32-1.96)	.62
>8	37	62	28	55	1.28 (0.71-2.27)	.42
Admission category						
Surgical	23	34	23	31	0.97 (0.36-2.63)	.96
Medical	67	94	63	92	1.23 (0.69-2.22)	.48
Colonization index ≥0.5[a]	70	101	70	99	0.93 (0.54-1.59)	.78
Corrected colonization index ≥0.4[b]	54	76	56	80	1.02 (0.56-1.89)	.94
Candida score ≥3	66	96	58	85	0.95 (0.55-1.67)	.87
(1-3)-ß-D-glucan, pg/mL[c]						
>250	14	21	17	25	0.96 (0.27-3.33)	.95
>80	61	91	58	84	0.98 (0.55-1.75)	.96
≤80	29	37	28	39	0.85 (0.27-2.63)	.78



Empirical Micafungin Treatment and Survival Without Invasive Fungal Infection in Adults With ICU-Acquired Sepsis, Candida Colonization, and Multiple Organ Failure. The EMPIRICUS Randomized Clinical Trial

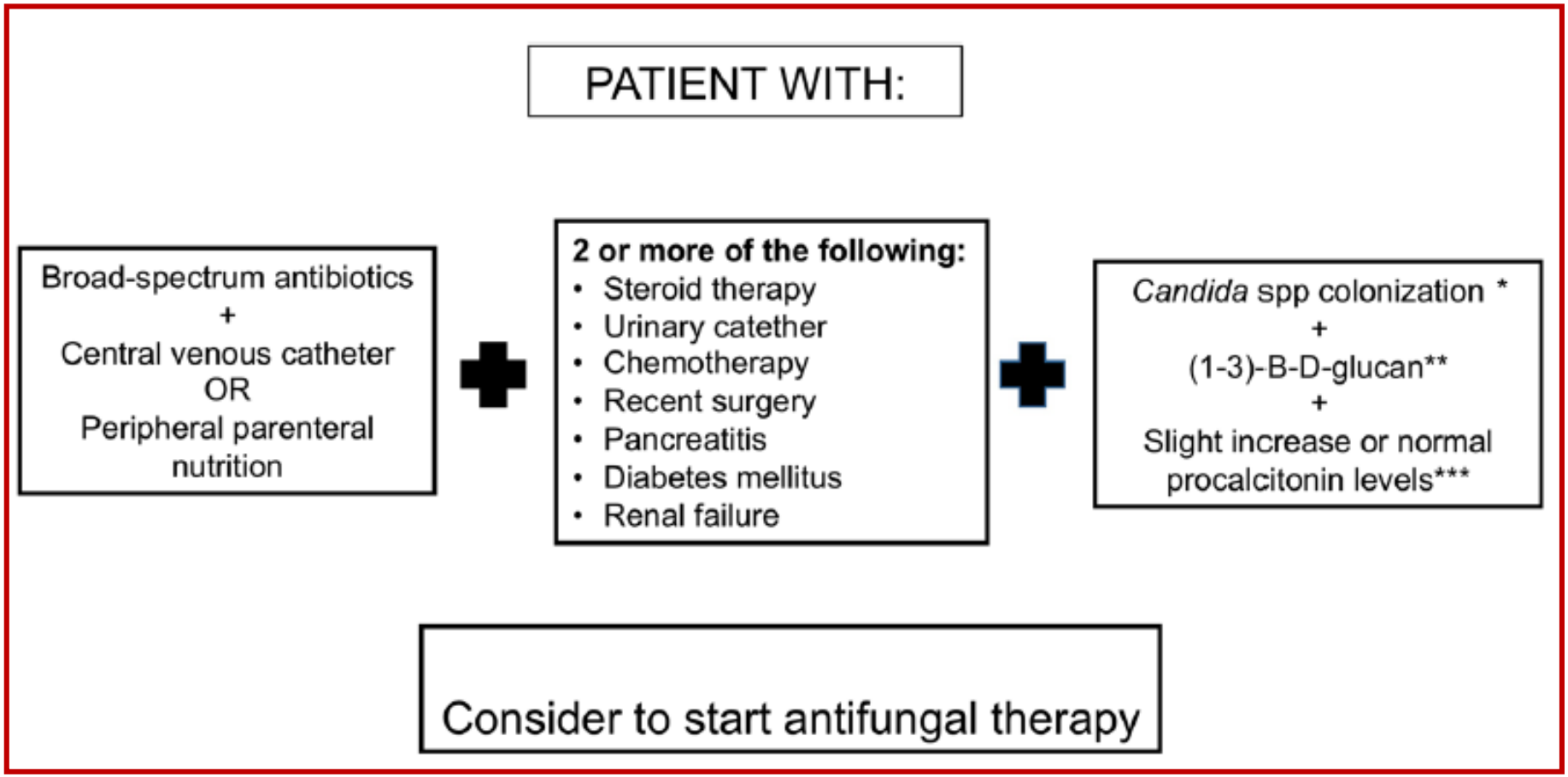
FJ Timsit et al, JAMA 2016

Among non-neutropenic critically ill patients with ICU-acquired sepsis, *Candida* species colonization at multiple sites, and multiple organ failure, empirical treatment with micafungin, compared with placebo, did not increase fungal infection–free survival at day 28.

Identification and management of invasive mycoses in internal medicine: a road-map for physicians

M. Falcone et al. Intern Emerg Med 2014

OUTSIDE THE ICU?



IL PROBLEMA CANDIDEMIA: APPROCCIO

MIRATO

	ESCMID 2012	ITALIC 2013	IDSA 2016
Primary therapy	ECH	ECH FLC in stable pts	ECH FLC in non critically-ill pts, unlikely to have a FLC-resistant Candida species
Alternative therapy	Lipid-AMB , VCZ, FLC	Lipid-AMB, VCZ	Lipid-AMB
Step-down oral therapy	After 10 days if patient stable, tolerates oral route and if yeast is susceptible	Encouraged in stable pts with susceptible Candida spp., but the exact time to shift is unknown	Recommended for pts with susceptible Candida isolates, demonstrated clinical stability, and have cleared the BSI
Optimal length of treatment in pts without organ involvement	14 days after clearance of BSI	14 days after clearance of BSI	14 days after clearance of BSI and resolution of symptoms
CVC removal	Strongly advised	Strongly advised	Strongly advised
Ophthalmoscopic investigation	Advised	Advised	Strongly advised
TTE/TOE	TOE advised	TTE/TOE advised in all pts with persistent candidemia (positive BC at 96 h despite adequate management) and follow-up 6 months	Not specified
Follow-up BC	Daily	Yes, timing not specified	Every day or every other day

28th ECCMID Madrid, Spain 21 – 24 April 2018

A bundle approach reduces mortality of patients with candidaemia: a multicentre pre-post study.

Sara Tedeschi*, Luigia Scudeller, Silvia Corcione, Raffaella Losito, Maria Merelli, Alessio Mesini, Roberto Angilletta, Francesca Raffaelli, Elena Rosselli Del Turco, Michele Bartoletti, Maddalena Giannella, Matteo Bassetti, Francesco Giuseppe De Rosa, Mario Tumbarello, Claudio Viscoli, Pierluigi Viale

**Infectious Disease Unit - Sant'Orsola Hospital, Bologna,*

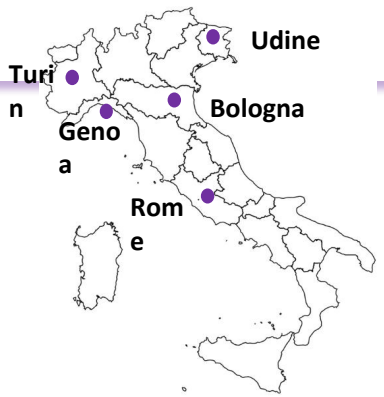
AIM

To create a working tool for clinicians caring for patients with candidaemia (a "candidaemia bundle" including drug choice, non-pharmacological management and clinical monitoring), to reduce variability in the management and to improve patient outcome.

STUDY DESIGN

Quasi experimental *pre-post* study at 5 Italian teaching hospitals

STUDY DESIGN



Quasi experimental *pre-post* study at 5 Italian teaching hospitals

1st Jan 2009 | **31st Dec 2012** | **1st Jan 2016** | **30th Jun 2017**

Retrospective *pre*-bundle phase

- Retrospective data collection
- All candidemia episodes identified through Microbiology database
- Patient managed by treating physicians according to local standard practice

Data analysis, bundle creation and implementation

Prospective *post*-bundle phase

- All candideamia episodes managed according to the bundle
- Prospective data collection

THE CANDIDEAEMIA BUNDLE

Alert to ID consultant team when blood cultures yielded *Candida* spp

OBJECTIVES

Primary objective

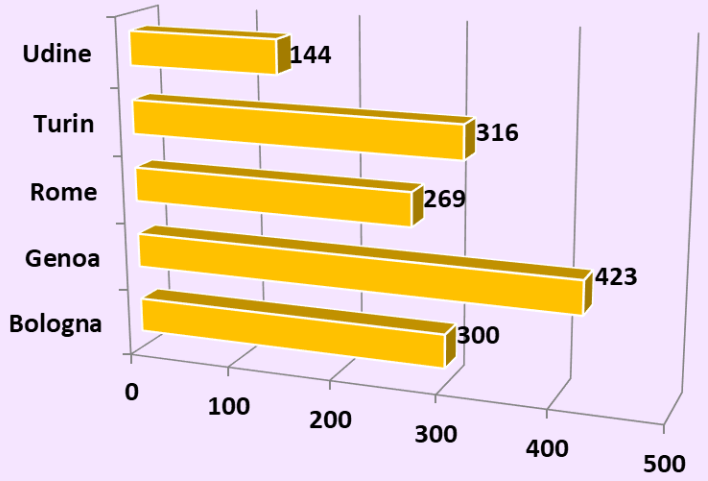
To compare in-hospital mortality before and after the implementation of the "candidaemia bundle".

Secondary objectives

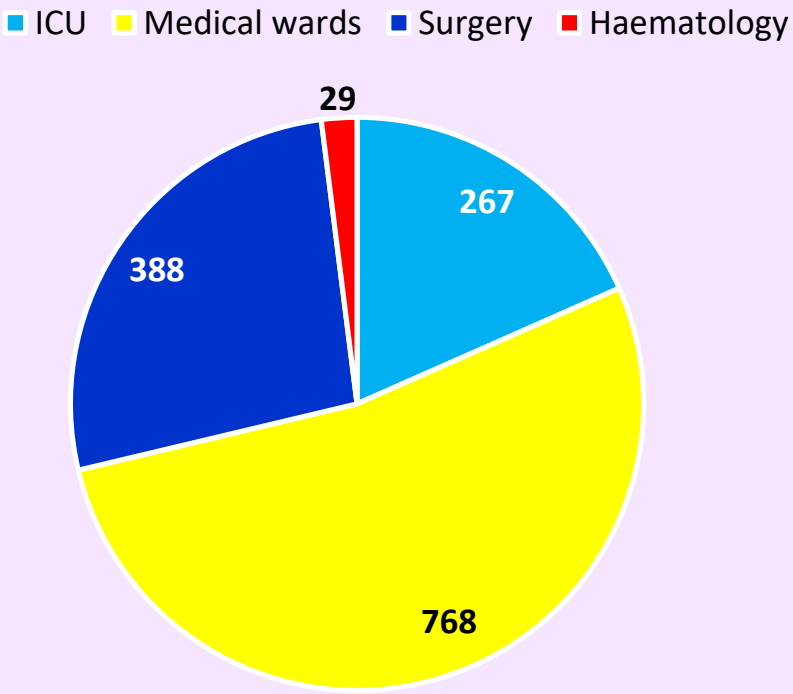
- To compare the two periods before and after the implementation of the bundle, in terms of candidaemia-related length of stay (from first positive blood culture to discharge/death).
- To describe *Candida* species epidemiology as causative agent of candidaemia and epidemiological trends.
- To assess risk factors for mortality among patients with candidaemia.
- To assess risk factors for initial inappropriate therapy (if associated to poorer outcome).

RESULTS: study population

- 1452 patients (*pre*-phase n=1030, *post*-phase n=422)
- 58% males, median age 72 years (IQR 60-80)



Distribution of candidaemia episodes in hospital wards



RESULTS: *pre*-phase *vs post*-phase

	All patients (n=1452)	*Pre*-phase (n=1030)	*Post*-phase (n=422)	p
Age (ys) – median (IQR)	72 (60-80)	70 (59-79)	75 (65-83)	<0.001
Predisposing factors – n° (%)				
Parenteral nutrition	810 (56)	632 (61)	178 (42)	<0.001
Diabetes	326 (22)	265 (26)	61 (14)	<0.001
Previous surgery	526 (36)	391 (38)	135 (32)	0.03
Solid cancer	442 (30)	360 (35)	82 (19)	<0.001
Chronic corticosteroids	259 (18)	210 (20)	49 (12)	<0.001
***Candida* albicans isolation** – n° (%)	850 (58)	641 (62)	209 (49.5)	<0.001
Fluconazole susceptibility – n° (%)	960 (83)	697 (88)	263 (71)	<0.001
Early CVC removal (n=1118) – n° (%)	562 (50)	387 (48)	175 (56)	0.013
First line echinocandin – n° (%)	523 (43.8)	294 (35)	229 (64)	<0.001
Length of antifungal treatment (days) - median (IQR)	11 (1-20)	12 (3-21)	10.5 (0-18)	0.003
Candidaemia-related lenght of stay (days) - median (IQR)	17 (7-33)	16 (7-31)	19 (8-37)	0.023

RESULTS: survival

1452 patients

165 excluded
(< 72h of observation after index BC)
- 126 died before BC results
- 20 transferred to another hospital
- 19 discharged to home

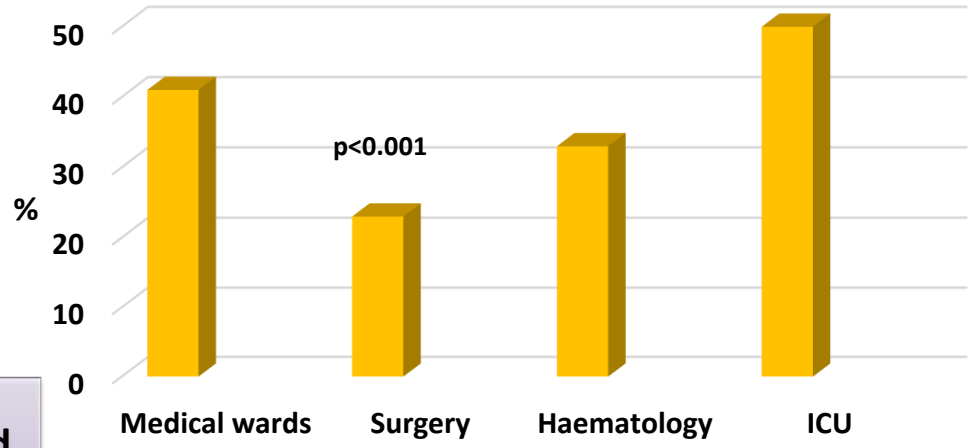
1287 patients considered for survival analysis

In-hospital 90-day mortality: 37.5%

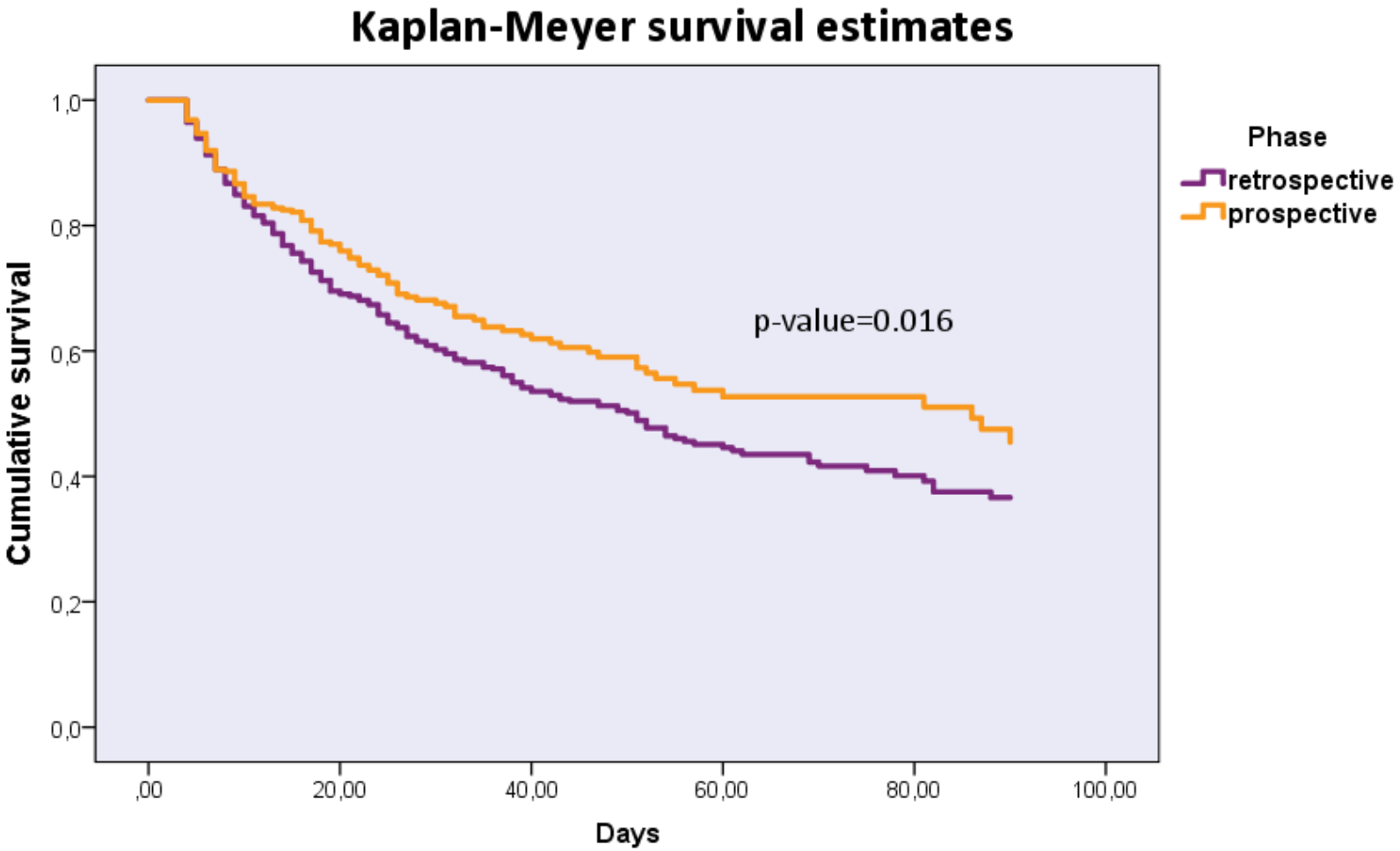
Pre-phase: 39%

Post-phase: 33.5%

Mortality rates in different hospital wards



RESULTS: survival



RESULTS: multivariate analysis of risk factors for mortality

	HR	95% CI	p
Age	1.034	1.026 – 1.042	<0.001
Diabetes	1.428	1.166 – 1.748	0.001
Liver cirrhosis	1.799	1.312 – 2.466	<0.001
Antibiotics in the previous 30 days	1.664	1.170 – 2.366	0.005
Chronic corticosteroids	1.421	1.139 – 1.773	0.002
Hospitalization in surgical ward	**0.599**	**0.464 – 0.774**	**<0.001**
Appropriate first-line antifungal drug	**0.724**	**0.563 – 0.931**	**0.01**
***Post*-phase**	**0.730**	**0.591 – 0.901**	**0.003**

CONCLUSIONS

- **Characteristics of the study population consistent with literature:**
  - Significant burden of candidaemia outside the ICU
  - High mortality (41%) in medical wards
  - Better outcome for patients hospitalized in surgical wards

OUR BUNDLE WAS EFFECTIVE IN IMPROVING SURVIVAL IN A LARGE COHORT OF HOSPITALIZED PATIENTS WITH CANDIDAEMIA

- **Further analysis are planned to investigate the impact of the compliance with each element of the bundle on patients' survival.**

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